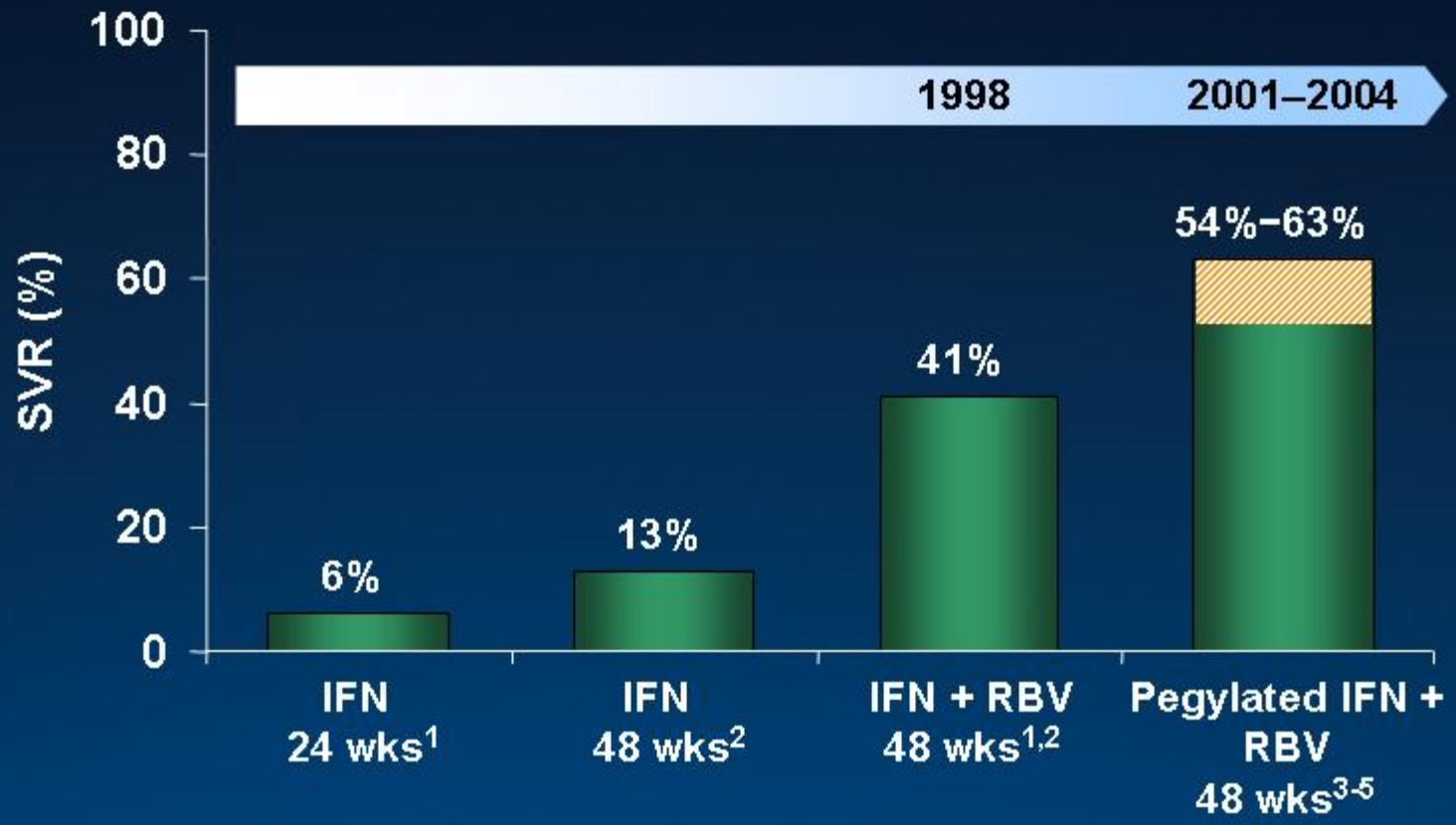
New Treatment Strategies (and Drugs) for HCV

Teaching Old Dogs New Tricks

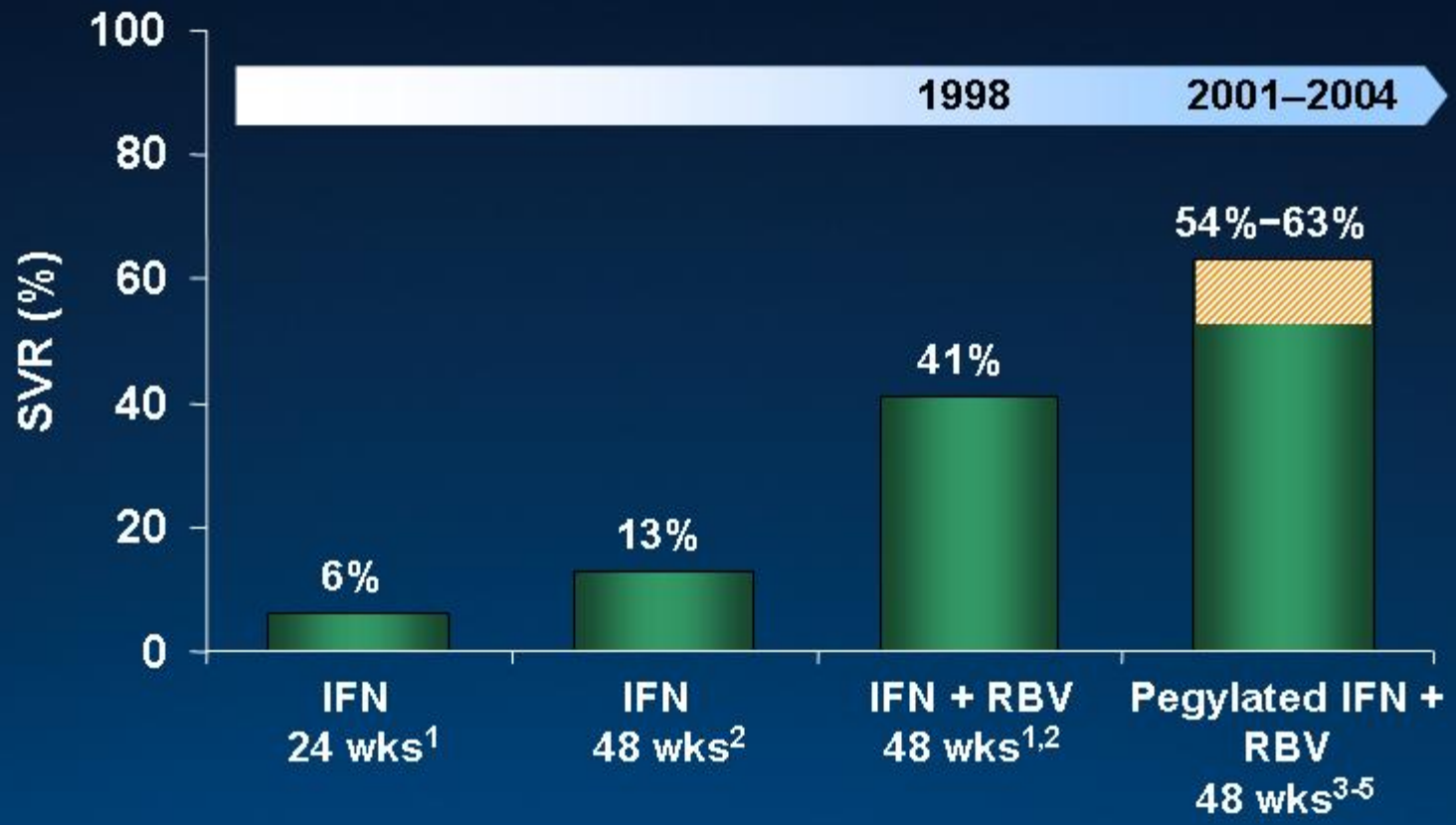
Terry D. Box, MD

Treatment Evolution of Hepatitis C Therapy



[1]McHutchison J, et al. *N Engl J Med*. 1998;339:1485-1492.; [2]Poynard T, et al. *Lancet*. 1998;352:1426-1432; [3]Manns M, et al. *Lancet*. 2001;358:958-965; [4]Fried MW, et al. *N Engl J Med*. 2002;347:975-982; [5]Hadziyannis S, et al. *Ann Intern Med*. 2004;14:346-355.

Treatment Evolution of Hepatitis C Therapy



[1]McHutchison J, et al. *N Engl J Med*. 1998;339:1485-1492.; [2]Poynard T, et al. *Lancet*. 1998;352:1426-1432; [3]Manns M, et al. *Lancet*. 2001;358:958-965; [4]Fried MW, et al. *N Engl J Med*. 2002;347:975-982; [5]Hadziyannis S, et al. *Ann Intern Med*. 2004;14:346-355.

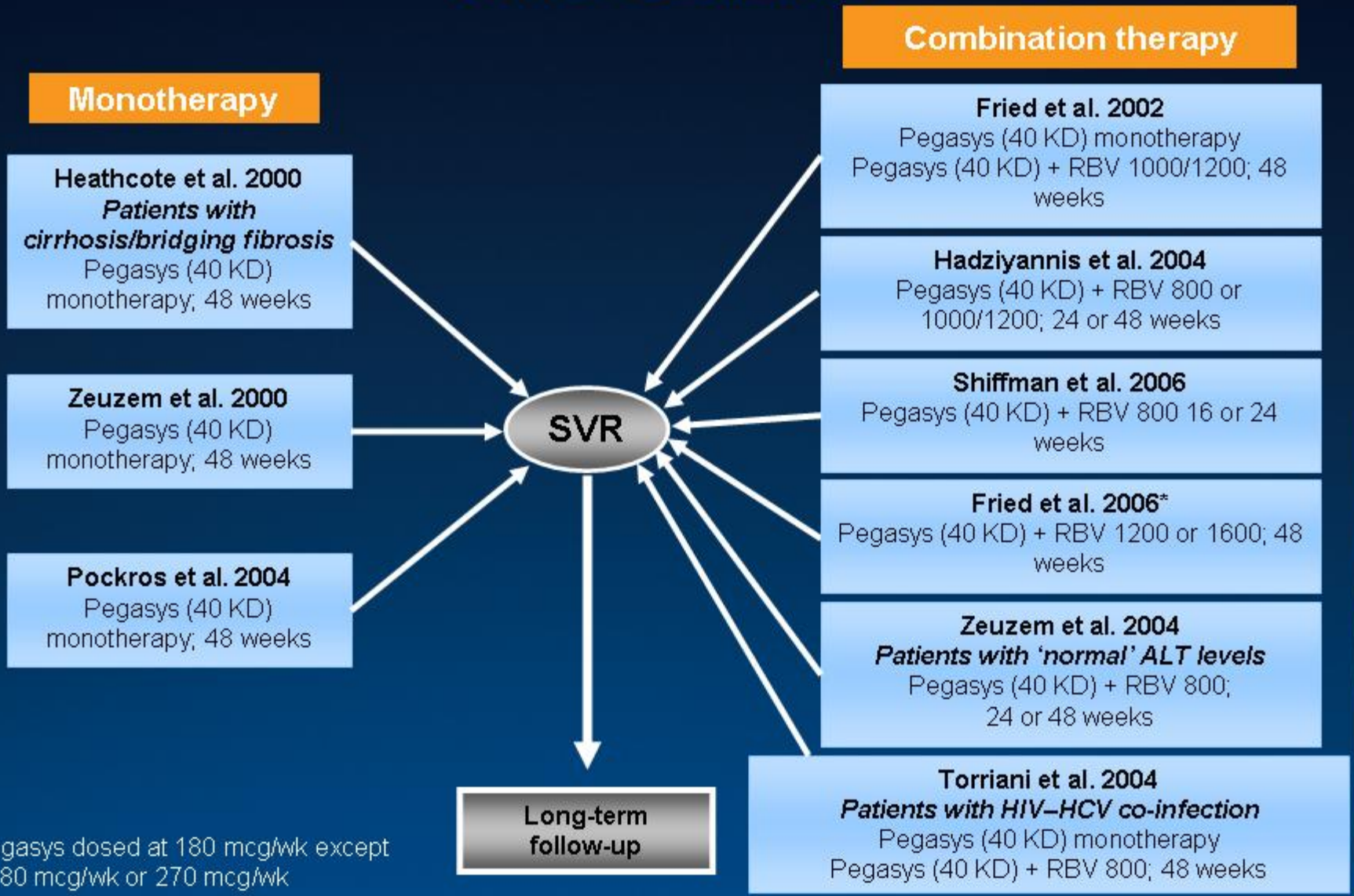
Durable SVR After Treatment With Pegasys: *Study Overview*

- Data from 9 randomized, multicenter trials were analyzed to quantify the long-term durability of an SVR
- 997 patients who achieved an SVR* are undergoing follow-up
  - 163 patients received Pegasys monotherapy
  - 741 patients received Pegasys and ribavirin
  - 93 HIV-HCV co-infected patients received Pegasys ± ribavirin
- Patient inclusion criteria
  - No further treatment after initial course of therapy
  - Annual testing for 5 years for HCV RNA in serum (COBAS AMPLICOR)

*SVR defined as undetectable HCV RNA (< 50 IU/mL) at 24 weeks' follow up

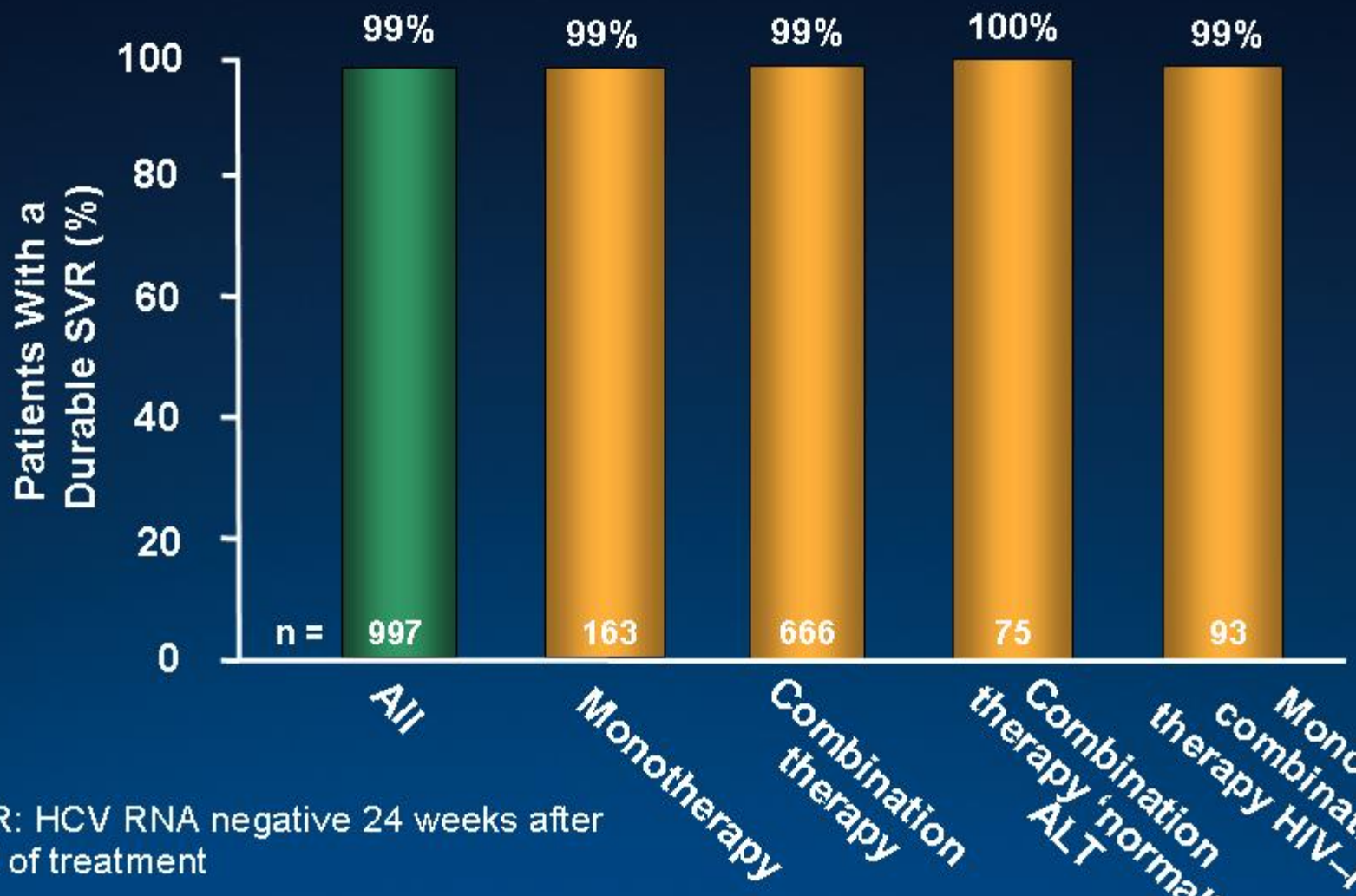
Swain M, et al. Presented at EASL 2007. April 11-15, 2007. Barcelona, Spain. Abstract 1.

Patient Recruitment From Nine Studies



Pegasys dosed at 180 mcg/wk except
* 180 mcg/wk or 270 mcg/wk

Patients With a Durable SVR at Mean 4.1 (0.4 to 7) Years Follow-up



SVR: HCV RNA negative 24 weeks after end of treatment

Swain M, et al. Presented at EASL 2007. April 11-15, 2007. Barcelona, Spain. Abstract 1.

Durable SVR After Treatment With Pegasys: *Conclusion*

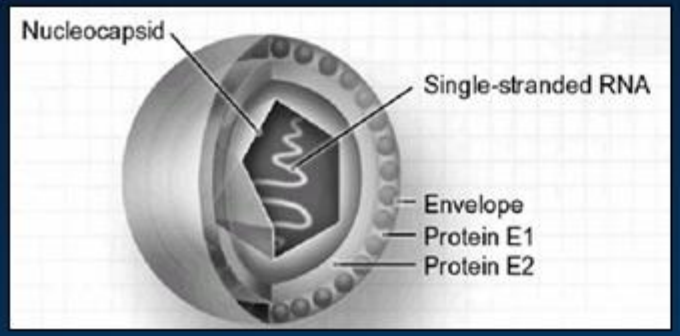
- Overall, 99% of patients (n = 997) who achieved an SVR remained HCV RNA undetectable at a mean of 4.1 (0.4–7) years follow-up
- 8 patients (0.8%) who achieved an SVR became HCV RNA-positive a mean 2 (1.1–2.9) years after completing therapy
- It is currently unclear whether patients who became HCV RNA detectable during follow-up experienced re-infection, rather than virological relapse

Swain M, et al. Presented at EASL 2007. April 11-15, 2007. Barcelona, Spain. Abstract 1.

Predictors of Virologic Response

Viral Factors

- Genotype
- Viral Load



Social Factors

- Adherence
- Mental health issues
- Substance use

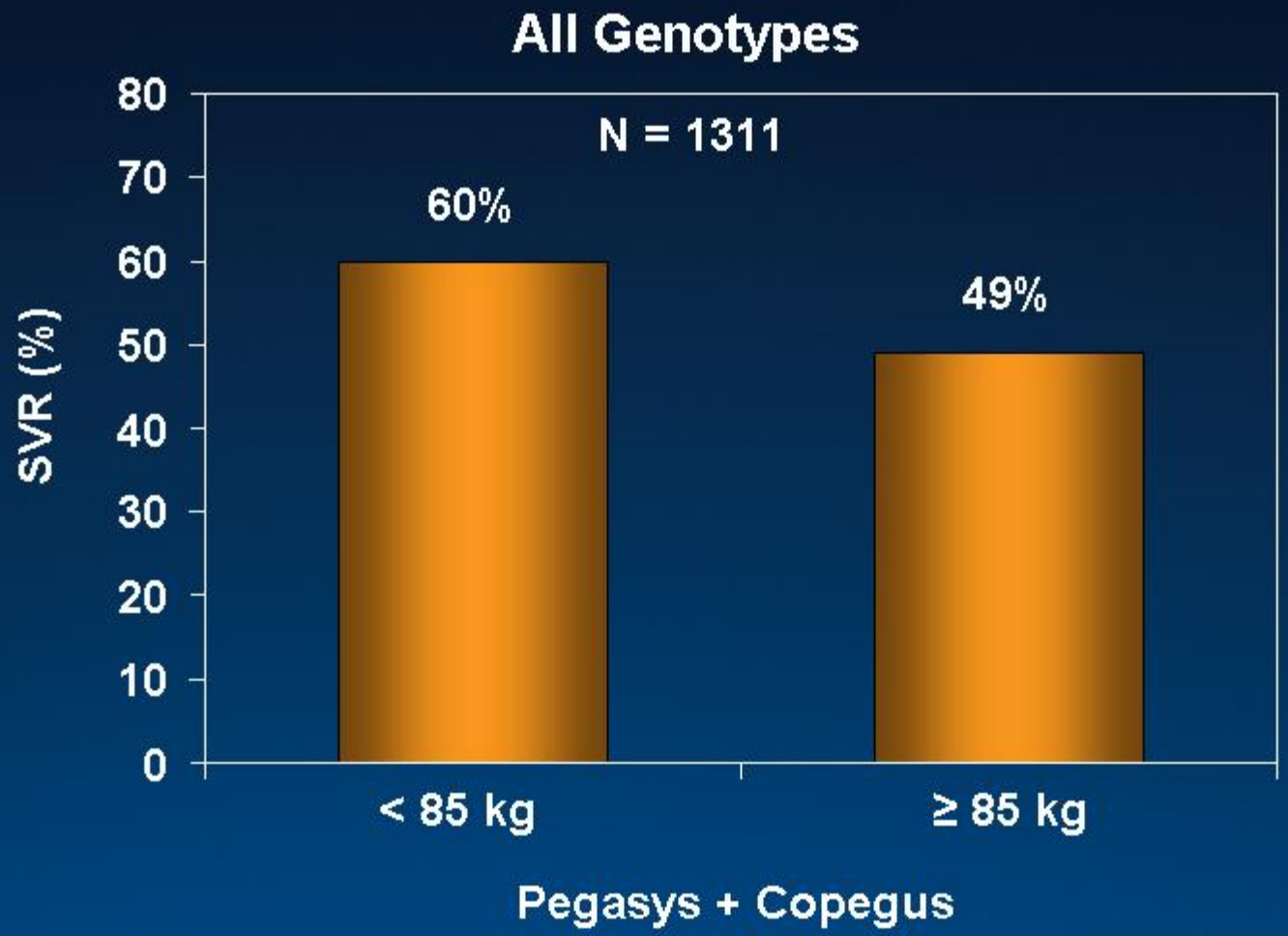
Host Factors

- Age
- Cirrhosis
- Coinfection (HIV, HBV)
- Gender
- Hepatic Fe Overload
- Hyperinsulinemia
- Race
- Steatosis
- Weight

Ferenci P. *Semin Liver Dis*. 2004;24:25-31.
NIH Consensus Development Conference Statement. *Gastroenterology*. 2002;123:2082-2099.

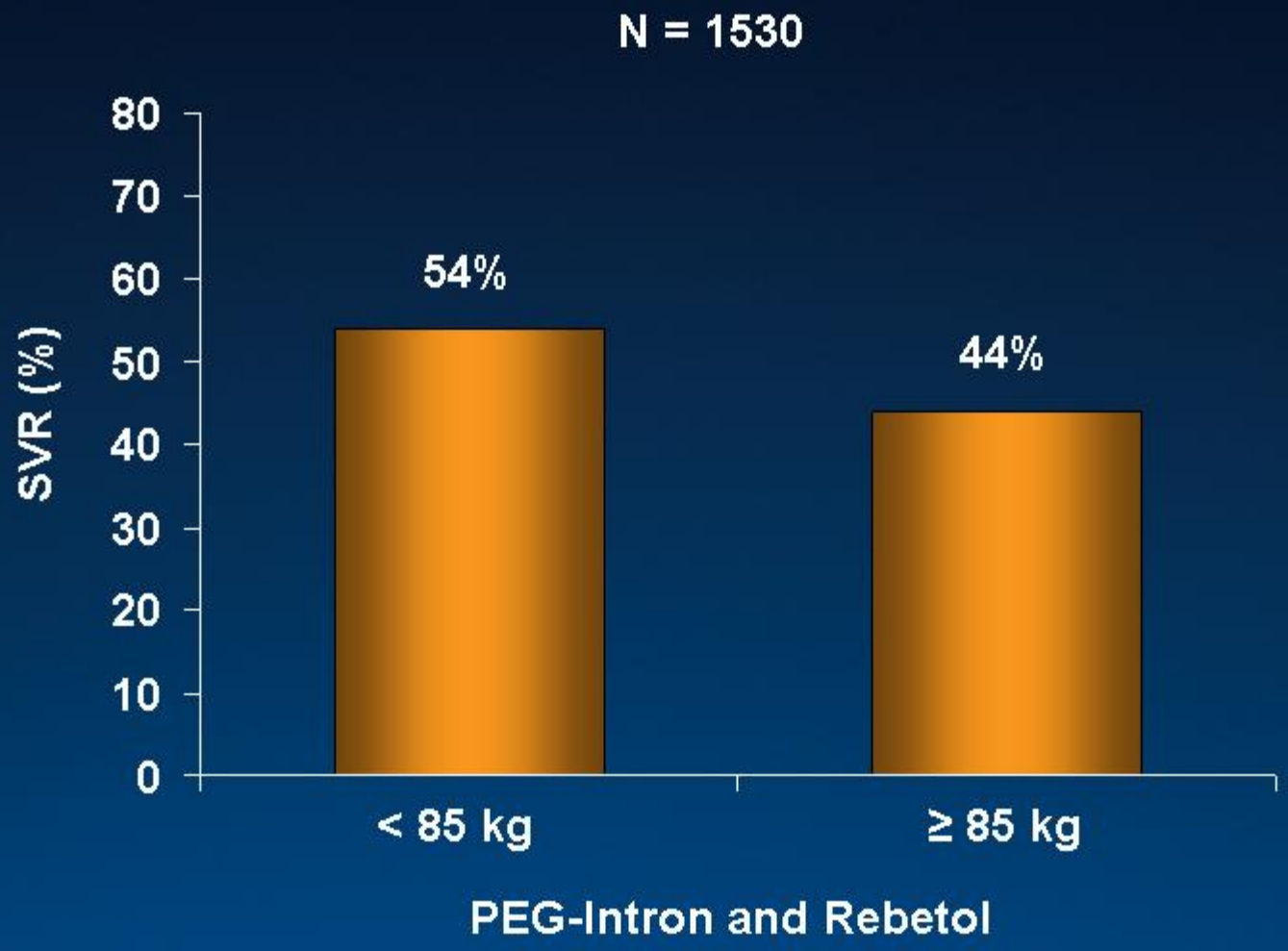
Impact of Weight and Metabolic Complications

SVR Rates in Lighter vs Heavier Patients: Pegasys



Pegasys (Peginterferon alfa-2a) [package insert]. Hoffmann-La Roche Inc. Nutley, NJ.

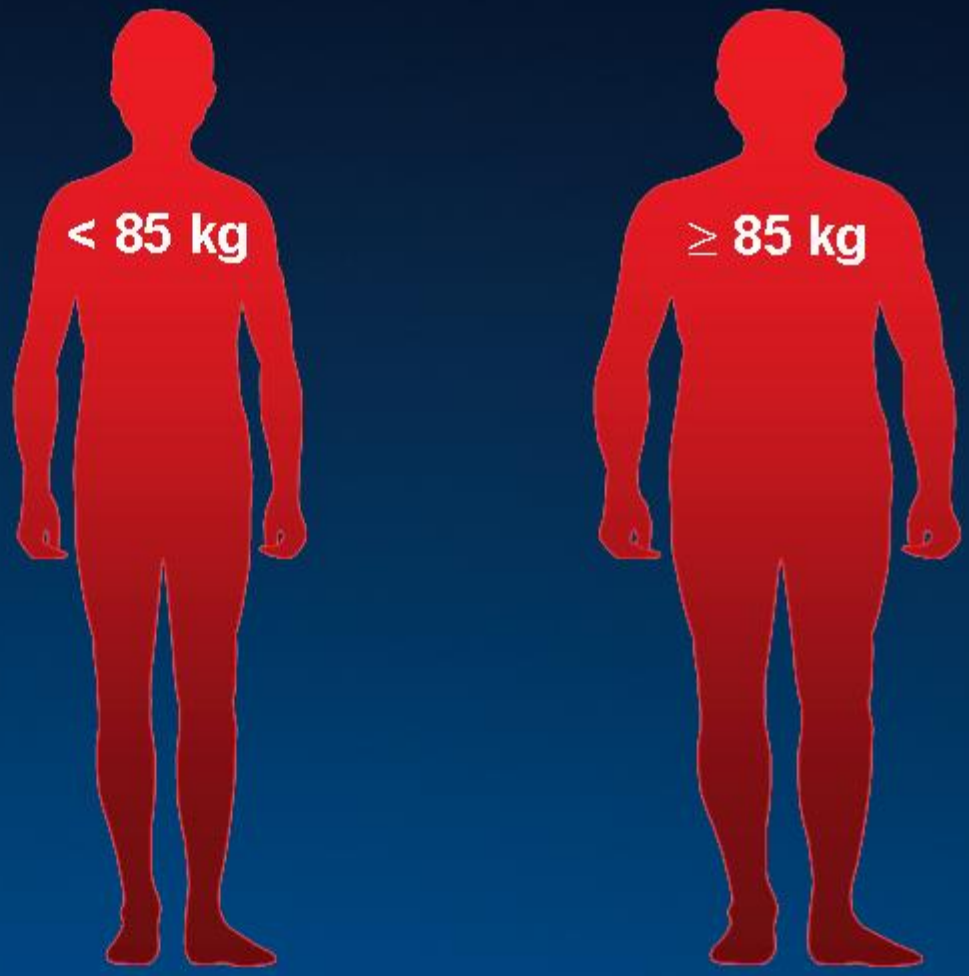
SVR Rates in Lighter vs Heavier Patients: PEG-Intron



Manns M, et al. *Lancet.* 2001;358:958-965.

Conclusion: Dosing in Lighter vs Heavier Patients

Regardless of product or dosing strategy, heavier patients demonstrate decreased response rates compared with lighter patients



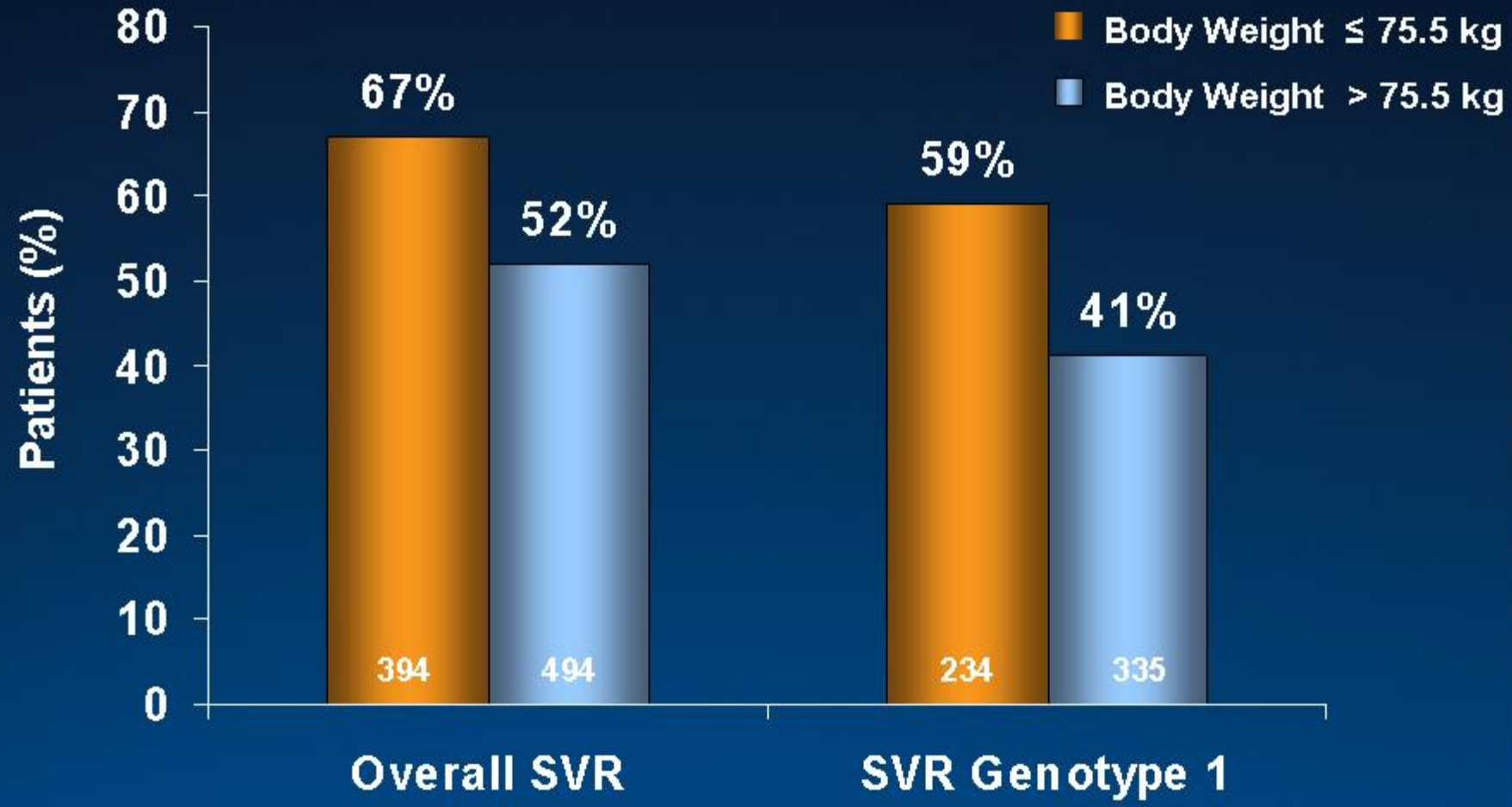
Foster G. *Aliment Pharmacol Ther.* 2004;20:825-830.

Clustering of Poor Prognostic Factors in Heavy Patients

- Retrospective analysis of the relationship between body weight and baseline factors, and between body weight and outcomes
- 2,404 patients treated with Pegasys and ribavirin[1-3]
- Stratified by weight
  - ≤ 75.5 kg (n = 1,143)
  - > 75.5 kg (n = 1,261)

[1]Swain M, et al. *AASLD*. Nov 11-15, 2005. San Francisco, CA. Abstract 67076.
[2]Hadziyannis S, et al. *Ann Intern Med*. 2004;140:346-355.
[3]Fried M, et al. *N Engl J Med*. 2002;347(13):975-982.

Clustering of Poor Prognostic Factors: SVR Rates by Body Weight



Swain M, et al. *AASLD*. Nov 11-15, 2005. San Francisco, CA. Abstract 67076.

Clustering of Poor Prognostic Factors in Heavy Patients: Summary

- Significantly higher prevalence of the following prognostic factors were seen in patients weighing > 75.5 vs < 75.5 kg
  - Male
  - Older
  - Black
  - Infection with HCV genotype 1
  - Higher serum HCV RNA level
  - Bridging fibrosis/cirrhosis
- Clustering of poor prognostic factors in patients > 75.5 kg may explain, in part, lower SVR rates in heavier patients with all Interferon-based regimens

Swain M, et al. AASLD. November 11-15, 2005. San Francisco, CA. Abstract 67076.

HCV: Factors Influencing Response

Pegylated Interferon + Ribavirin

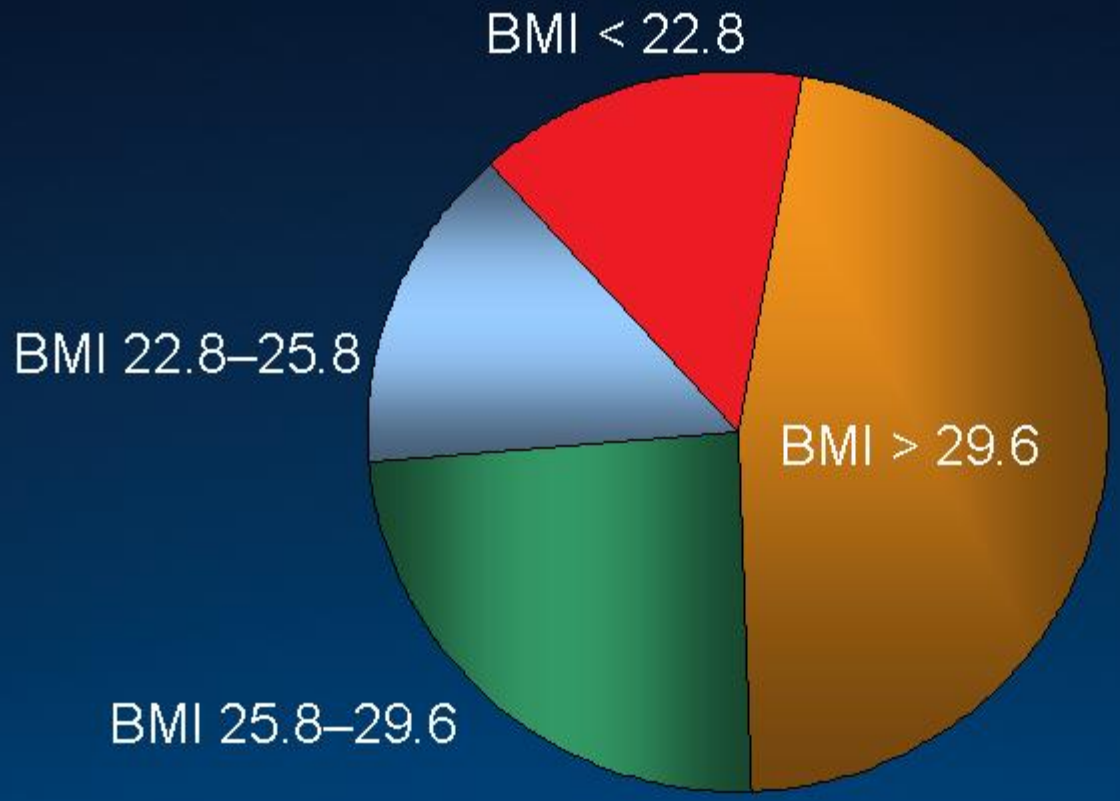
SVR: 54–63%

Factors Influencing Response to Current Antiviral Therapy

- Genotype
- Viral Load
- Age
- Duration of Infection
- Ethnicity
- Gender
- Fibrosis Stage
- Body Weight
- Steatosis/NASH
- Insulin Resistance

Fried M, et al. *N Engl J Med*. 2002;347:975-82.
Manns M, et al. *Lancet*. 2001;358:958-65.
Sanyal A, et al. *Am J Gastroenterol* . 2003;98:2064-71.
Poynard T, et al. *Hepatology*. 2003;38:75-85.

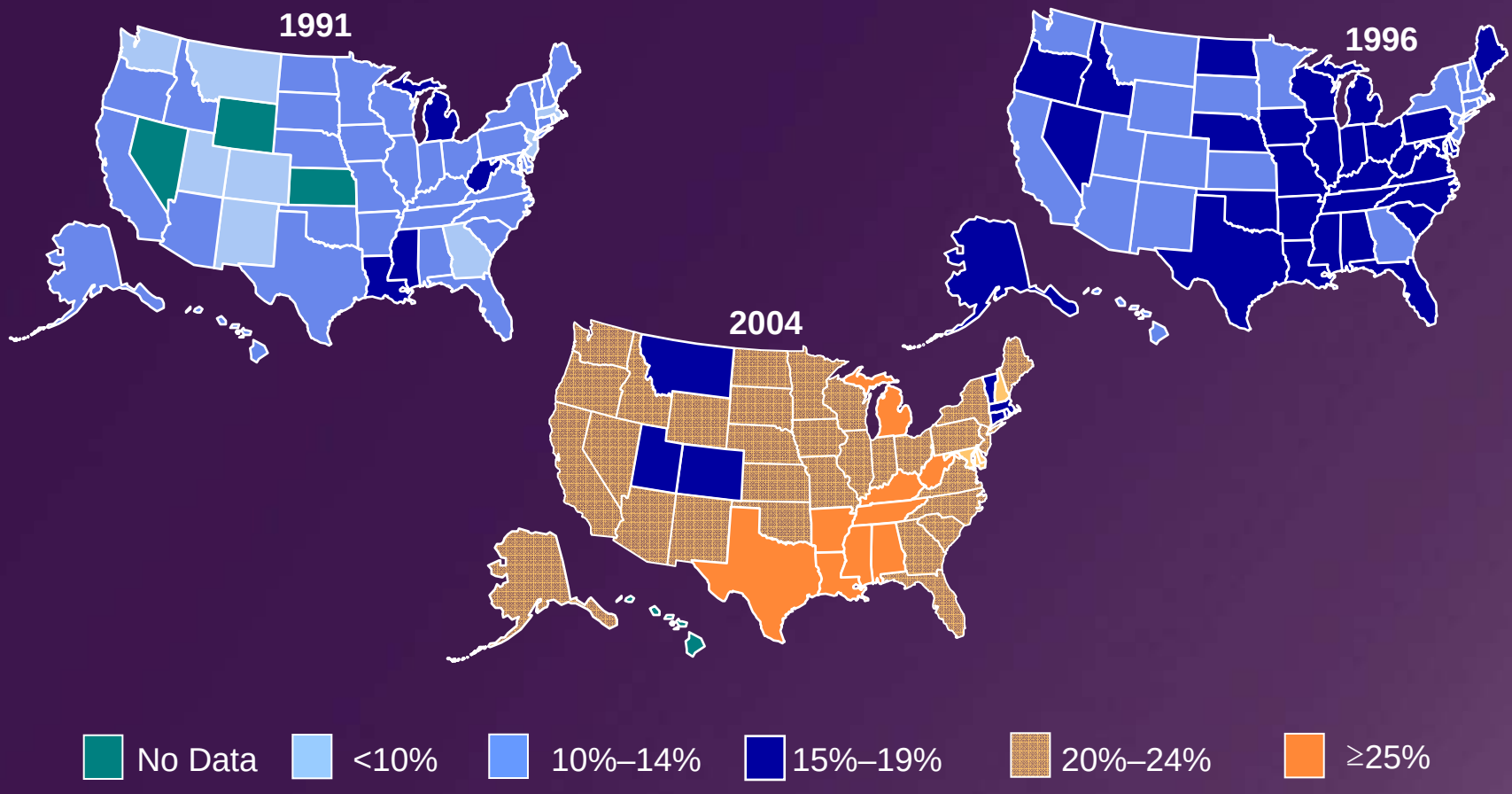
Correlation of Nonalcoholic Fatty Liver Disease to BMI in the US



Adapted from Ruhl C, et al. *Gastroenterology*. 2003;124:71-79

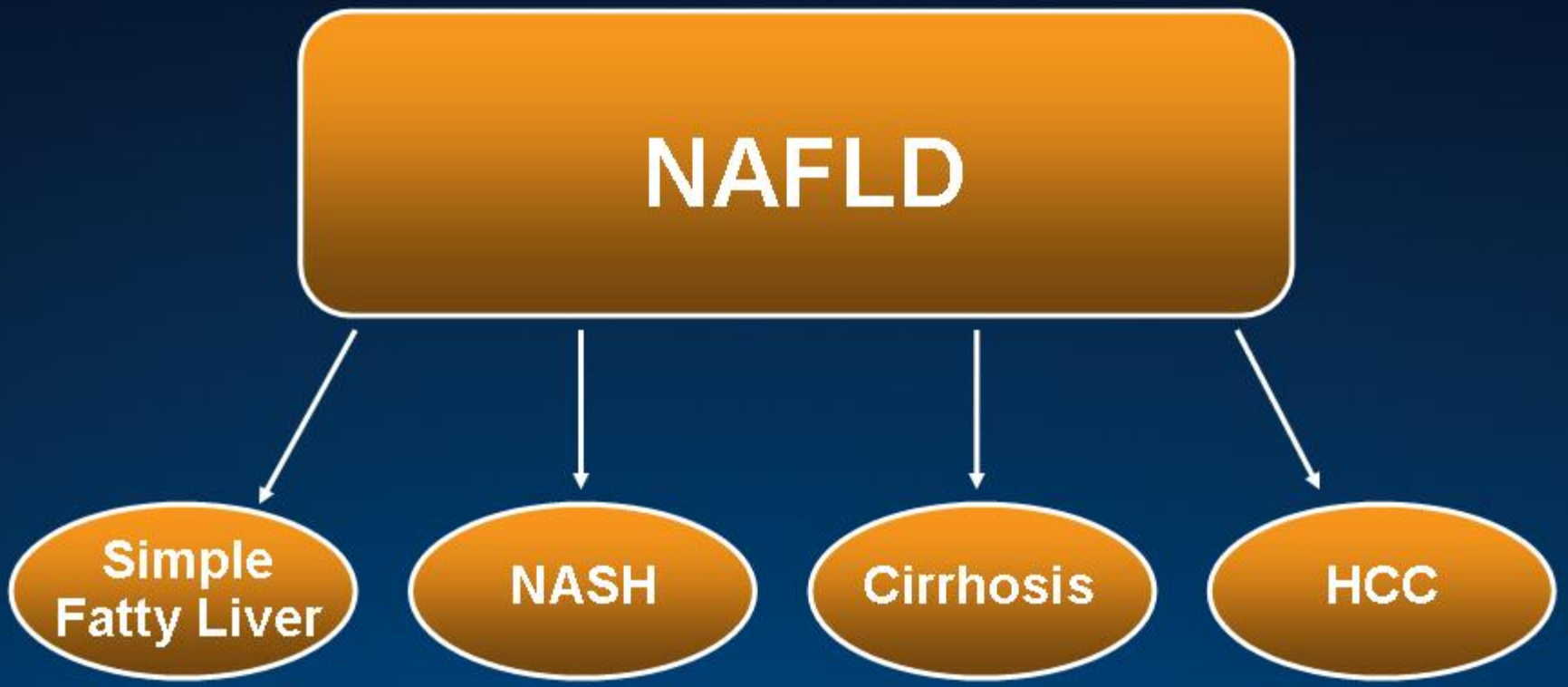
Prevalence of Obesity in the United States

Obesity Trends Among US Adults
Behavioral Risk Factor Surveillance System, 1991, 1996, 2004



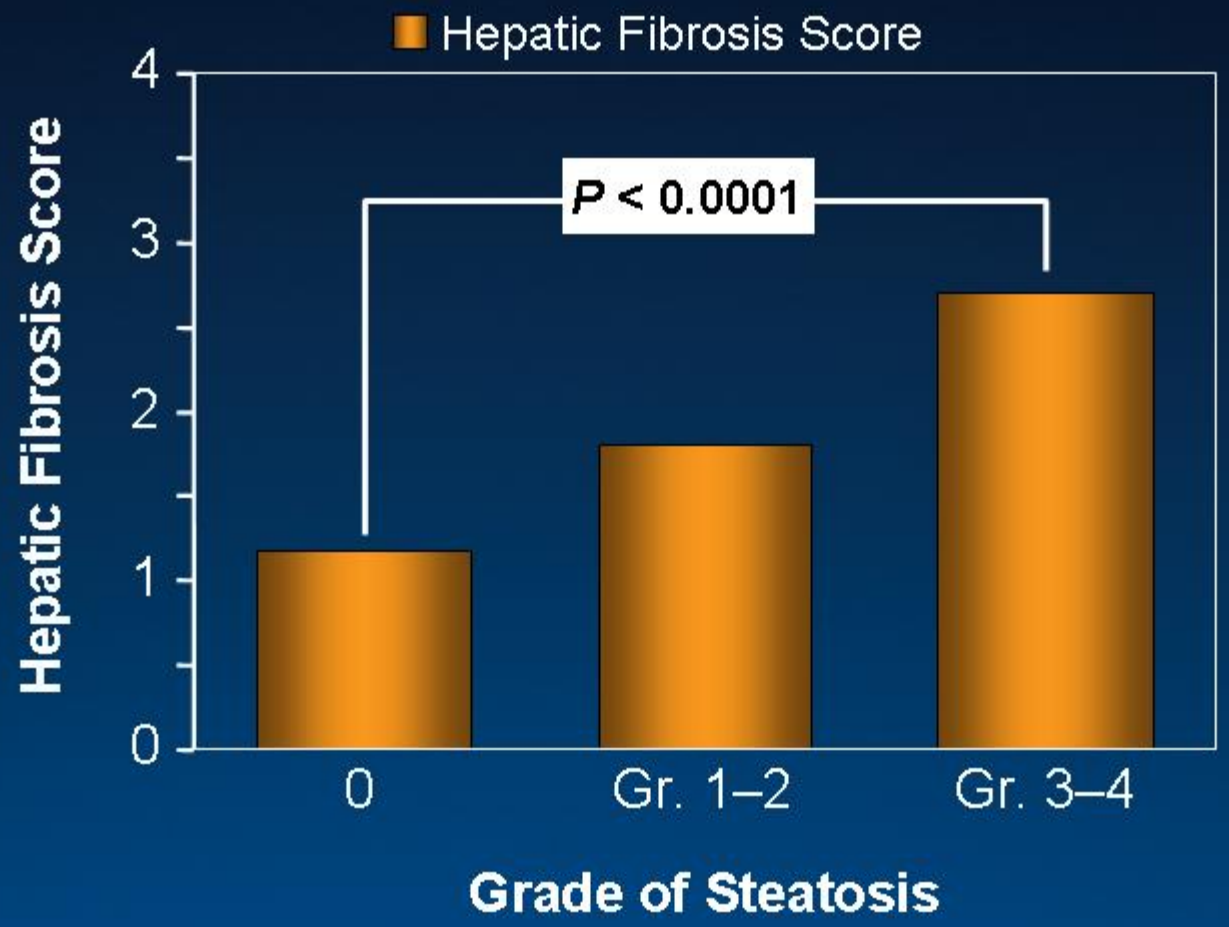
www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/obesity_trends_2005.ppt 5.

Clinical Progression of Non-Alcoholic Fatty Liver Disease (NAFLD)



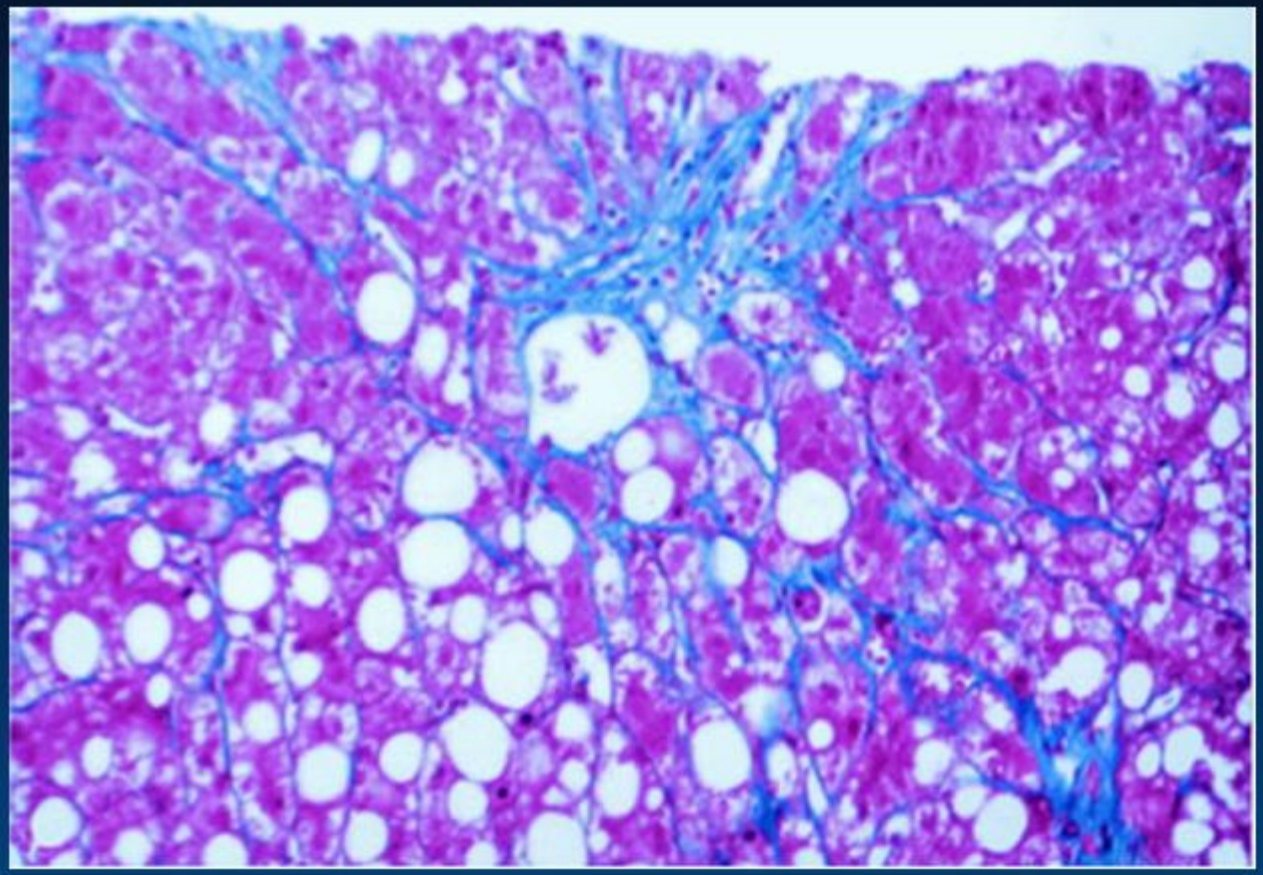
Farrell GC, et al. *Hepatology*. 2006;43(2 Suppl 1):S99-S112.

Association of Hepatic Steatosis and Fibrosis



Adinolfi L, et al. *Hepatology*. 2001;33(1):1358-1364.

Histopathology of Steatosis and NASH



Brunt EM, et al. *Mod Pathol*. 2003; 16:49-56.

Proposed Mechanisms for Co-Existent HCV and Steatosis

HCV
- Genotype 3
- Insulin Resistance

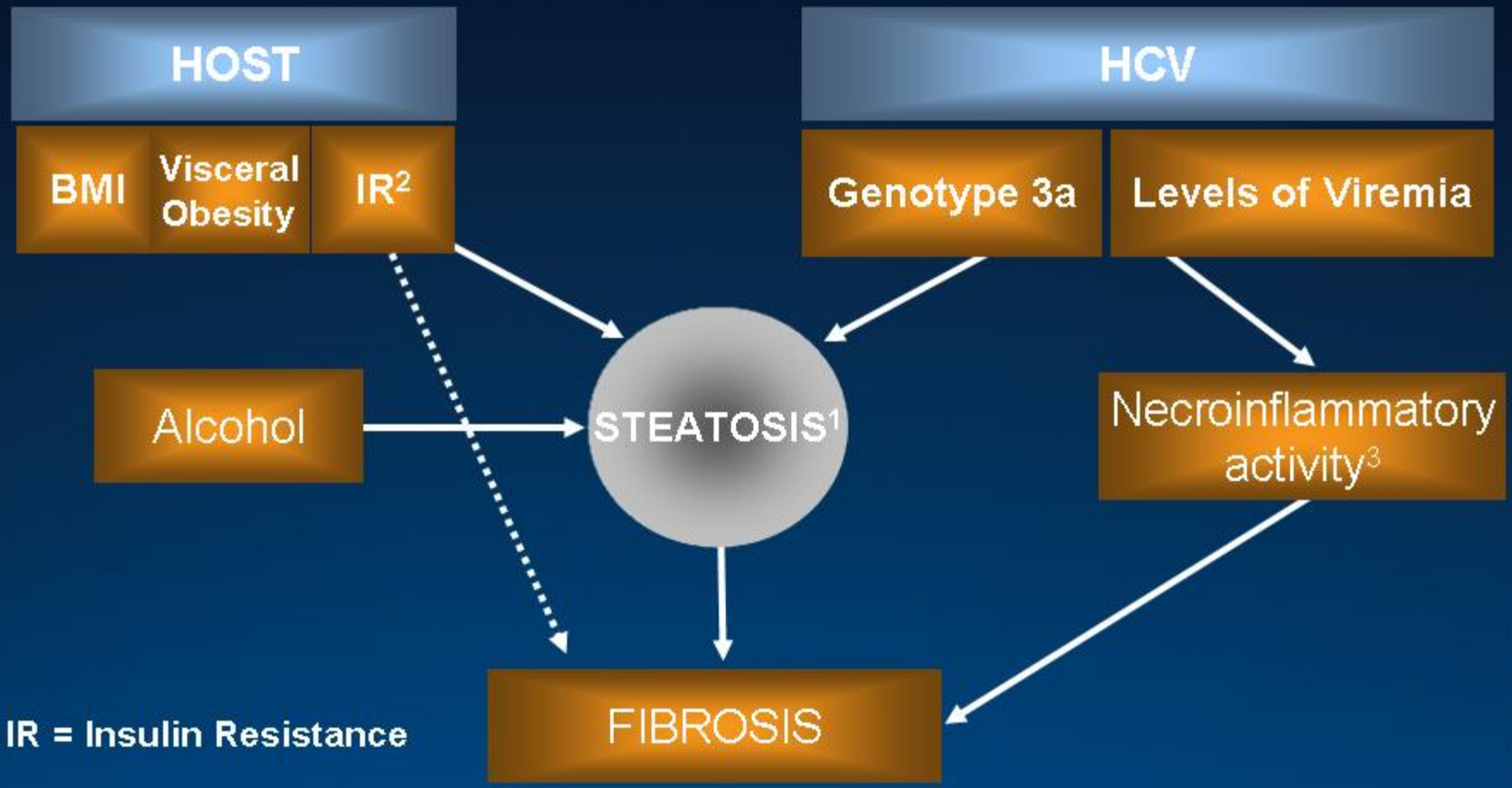
Host
- Obesity
- Diabetes Mellitus
- Insulin Resistance
- Alcohol Intake
- Medications

HCV + Steatosis

(50% of all HCV+ patients)

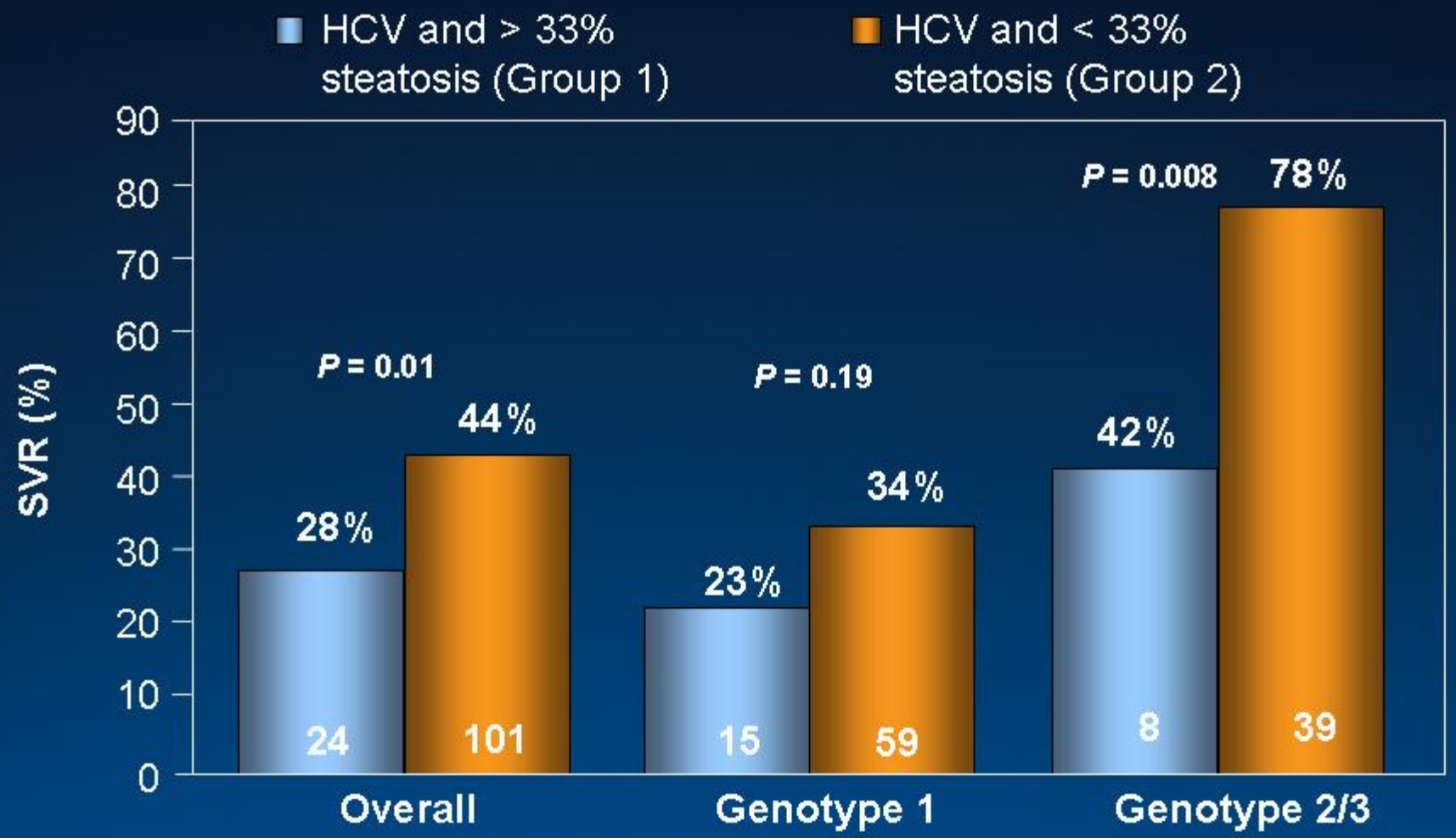
Patel K, et al. *Clin Liver Dis*. 2005 Aug 9(3):399-410.

Hypothesis of Events Associated With Steatosis and Fibrosis Progression



1. Adapted from Adinolfi L, et al. *Hepatology*. 2001;33(1):1358-1364.
2. Asselah T, et al. *Gut* . 2006;55:123-130.
3. Berson A, et al. *Gastroenterology*. 1998;114(4):764-774.

Decreased Response to Antiviral Therapy in HCV Patients With Coexistent Steatosis



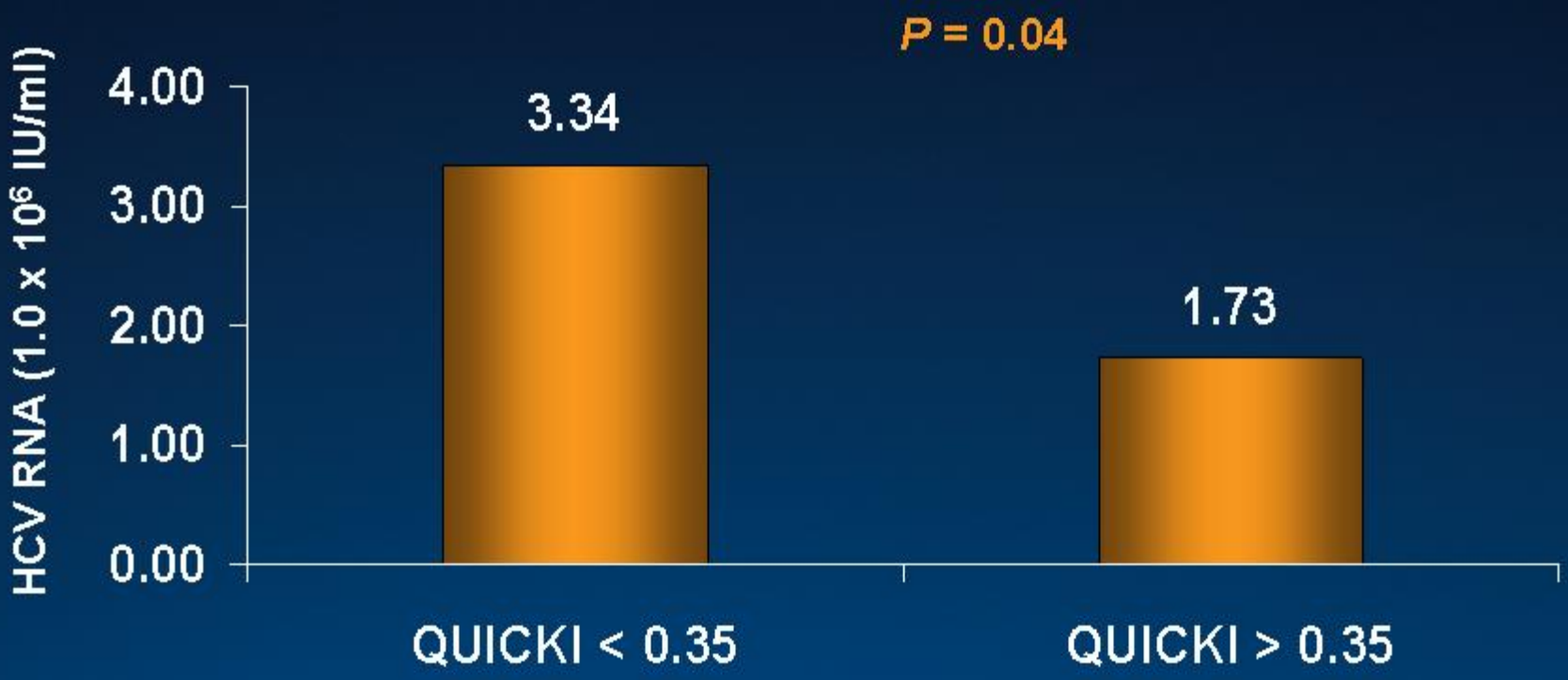
Harrison S, et al. *Clin Gastro and Hepat.* 2005;3:604-609.

Calculation of Insulin Resistance

- HOMA
  - Fasting insulin (µU/L) × Fasting glucose (mmol/L)

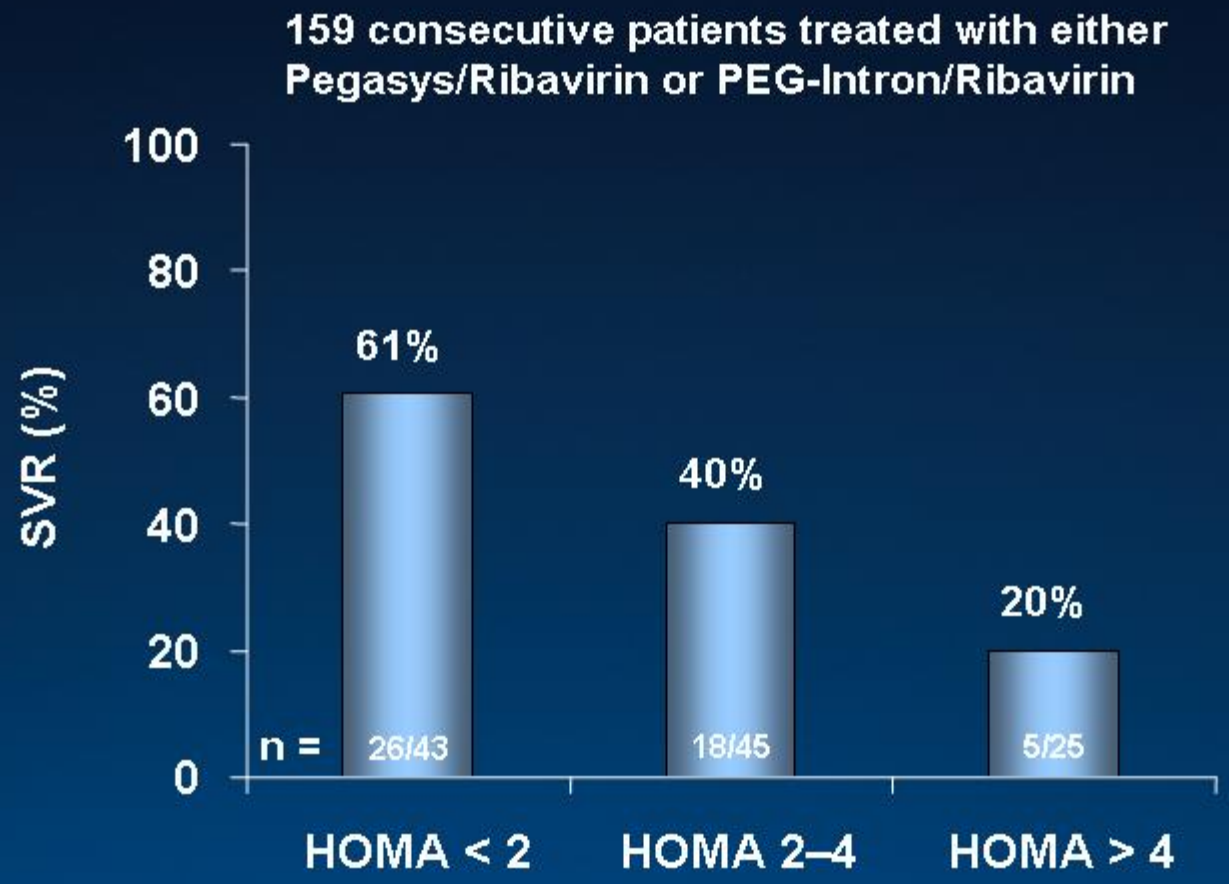
    22.5
    - *Remember to convert glucose in mg/dL to mmol/L, divide glucose by 18*
    - Values >1.8 to 2.0 are c/w insulin resistance
- QUICKI
  - Fasting insulin (µU/L) × Fasting glucose (mg/dL)
  - Log, then 1/×
  - Values <0.35 are c/w insulin resistance
- Rough estimate: multiply fasting insulin × glucose: values >700 are usually consistent with insulin resistance

Impact of Insulin Resistance on HCV Viral Load



Harrison SA. *Hepatology*. 2006;43(5):1168.

Impact of Insulin Resistance on Virologic Response in Genotype 1



(HOMA < 2, 2–4, and > 4: odds ratio, 2.43; 95% CI, 1.41–4.20; *P* = 0.004)

HOMA = homeostasis model assessment

Romero-Gomez M, et al. *Gastroenterology*. 2005;128:636-641.

Impact of Steatosis and Insulin Resistance on the HCV Antiviral Effects of Interferon

Increased antiviral protein production in hepatocytes blocking HCV replication

Increased immune activation proteins enhancing innate and adaptive anti-HCV immunity

Impaired Hepatocyte Function
Steatosis
Fibrosis
Hyperinsulinemia

Altered Immune Response
Insulin Resistance
Metabolic Syndrome
Leptin Mediated Activity

ANTIVIRAL RESPONSE

Samuel S. *Clin Micro Rev.* 2001;14(4):778-809.
Ramesh S. and Sanyal A. *Sem Liv Dis.* 2004;24(4):399-413 .

Steatosis and Insulin Resistance Summary

- Increasing obesity has made fatty liver disease a public health problem in the Western world[1]
- There exists a cluster of prognostic factors in HCV among which patient's weight is just one[1]
- Steatosis is an important cofactor in accelerating hepatic fibrosis and in increasing necroinflammatory activity[2]
  - Host and viral factors contribute to pathogenesis of steatosis in HCV
- Insulin resistance may contribute to steatosis and fibrosis progression in chronic HCV infection[3]
- Patients with steatosis and insulin resistance are less likely to respond to all IFN-based regimens[4]

[1]Choudury J, et al. *Sem Liv Dis*. 2004;24(4):349-362.
[2]Adinolfi L, et al. *Hepatology*. 2001;33(1):1358-64.
[3]Patton H, et al. *J Hepatol*. 2004;40:484-490.
[4]Poynard T, et al. *Hepatology*. 2003;38:75-85.

Virologic Response Guided Therapy: Improving Treatment Outcomes

Virologic Response Guided Therapy

- New concepts
  - All responders are not the same
  - Treatment after non-detectability
- Refine terminology
- Reconsider “rules” re: duration of Rx

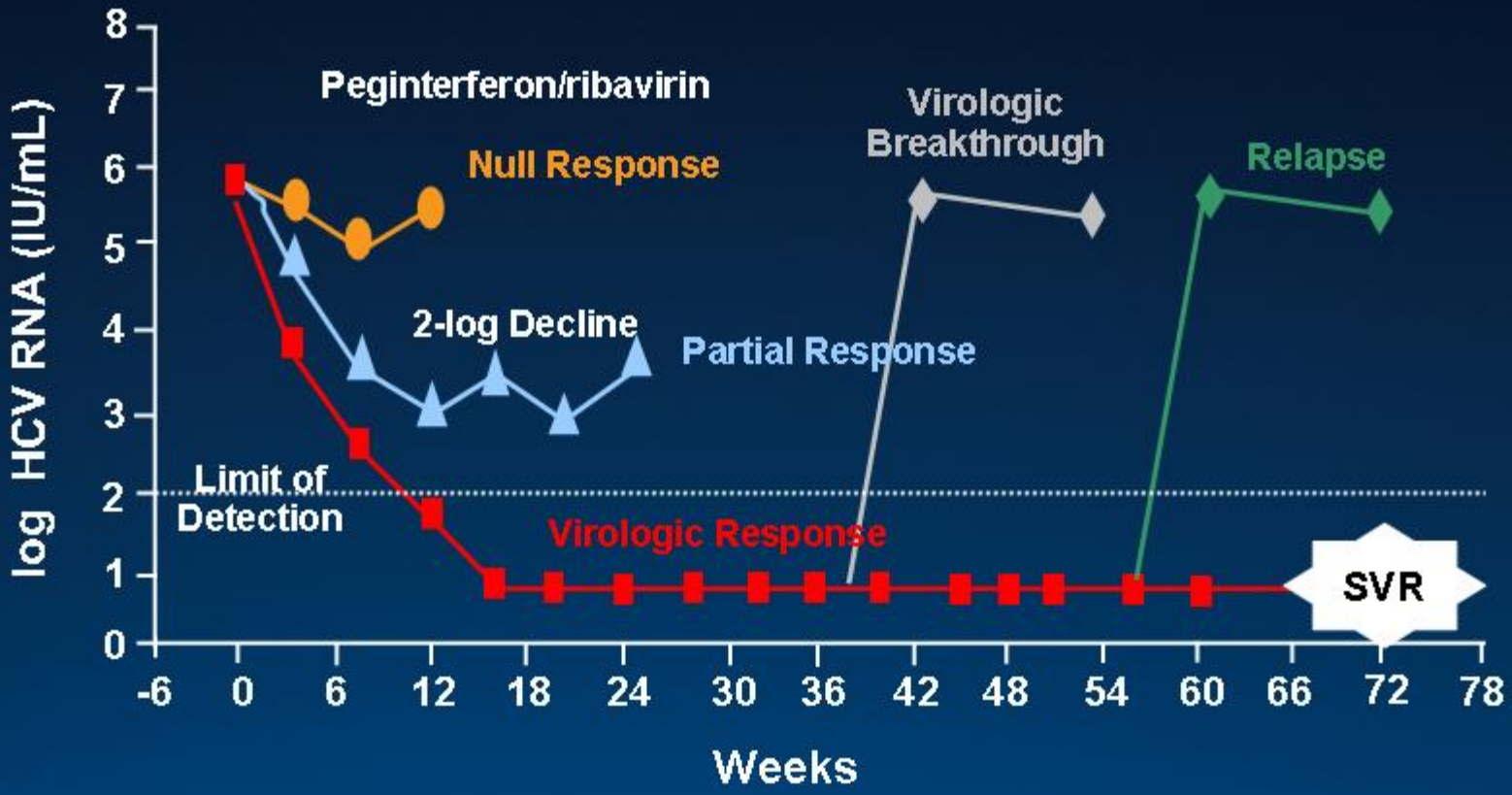
Pegasys Dosing Recommendations for Combination Therapy

- Medication supplied in *pre-filled syringes;* no reconstitution required
- Stable until expiration date if stored according to manufacturer's recommendations at 36° to 46°F and protected from light

Genotype	Pegasys Dose	Copegus Dose	Duration
Genotypes 1, 4	180 mcg QW	Patient weight: < 75 kg = 1000 mg ≥ 75 kg = 1200 mg	48 weeks 48 weeks
Genotypes 2, 3	180 mcg QW	800 mg	24 weeks

Pegasys (Peginterferon alfa-2a) [package insert]. Hoffmann-La Roche Inc. Nutley, NJ.

Patterns of Virologic Response During Treatment



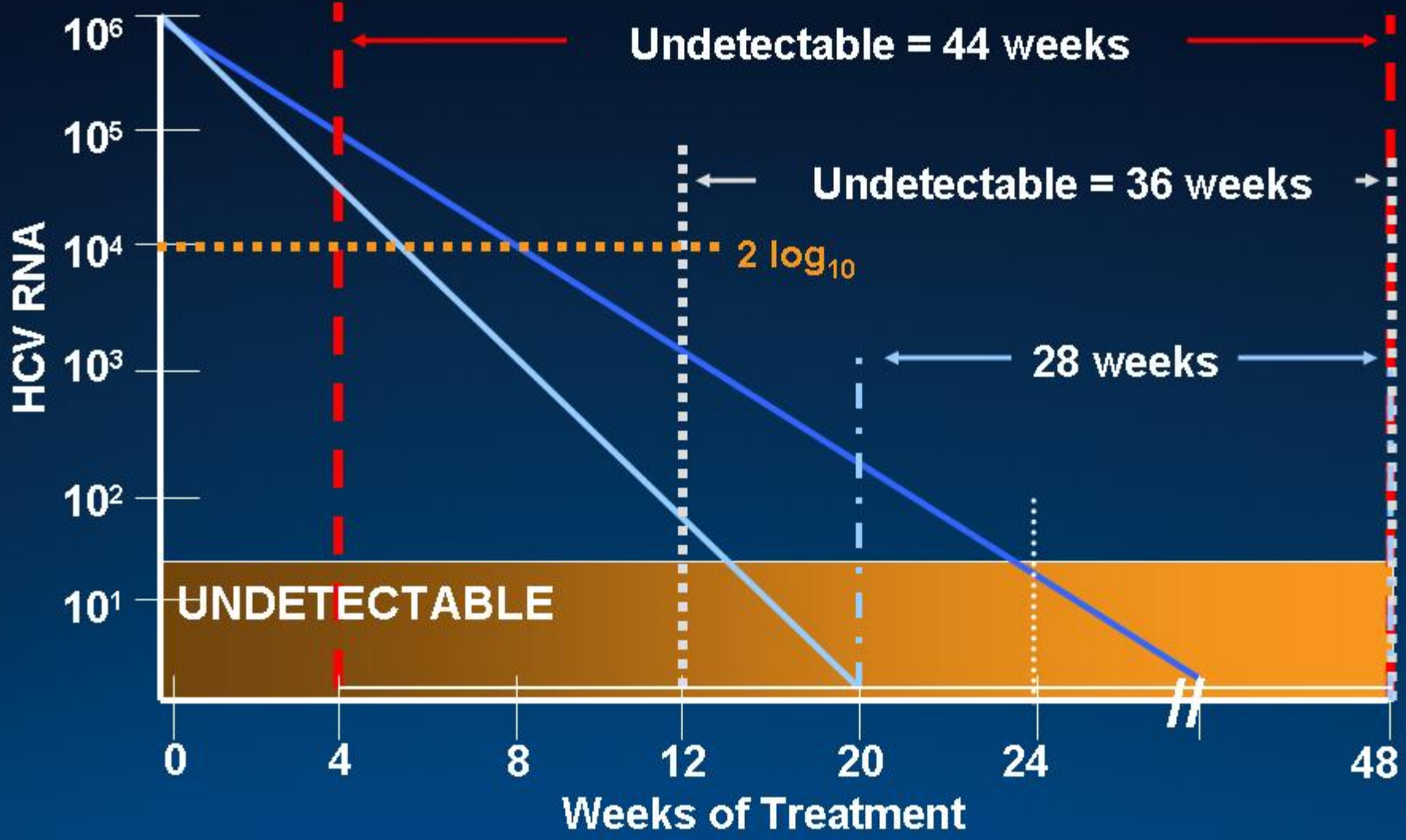
Shiffman M, et al. *Minerva Gastroenterol Dietol*. 2004;50(1):37-49.

Primary Reasons for Patients Failing PEG/RBV Therapy

- Inherent interferon resistance
- Non-compliance with treatment recommendations
- Adverse events resulting in dose reductions or discontinuations
- Response/Nonresponse not recognized due to inappropriate or inadequate HCV RNA monitoring
- Insufficient duration of therapy

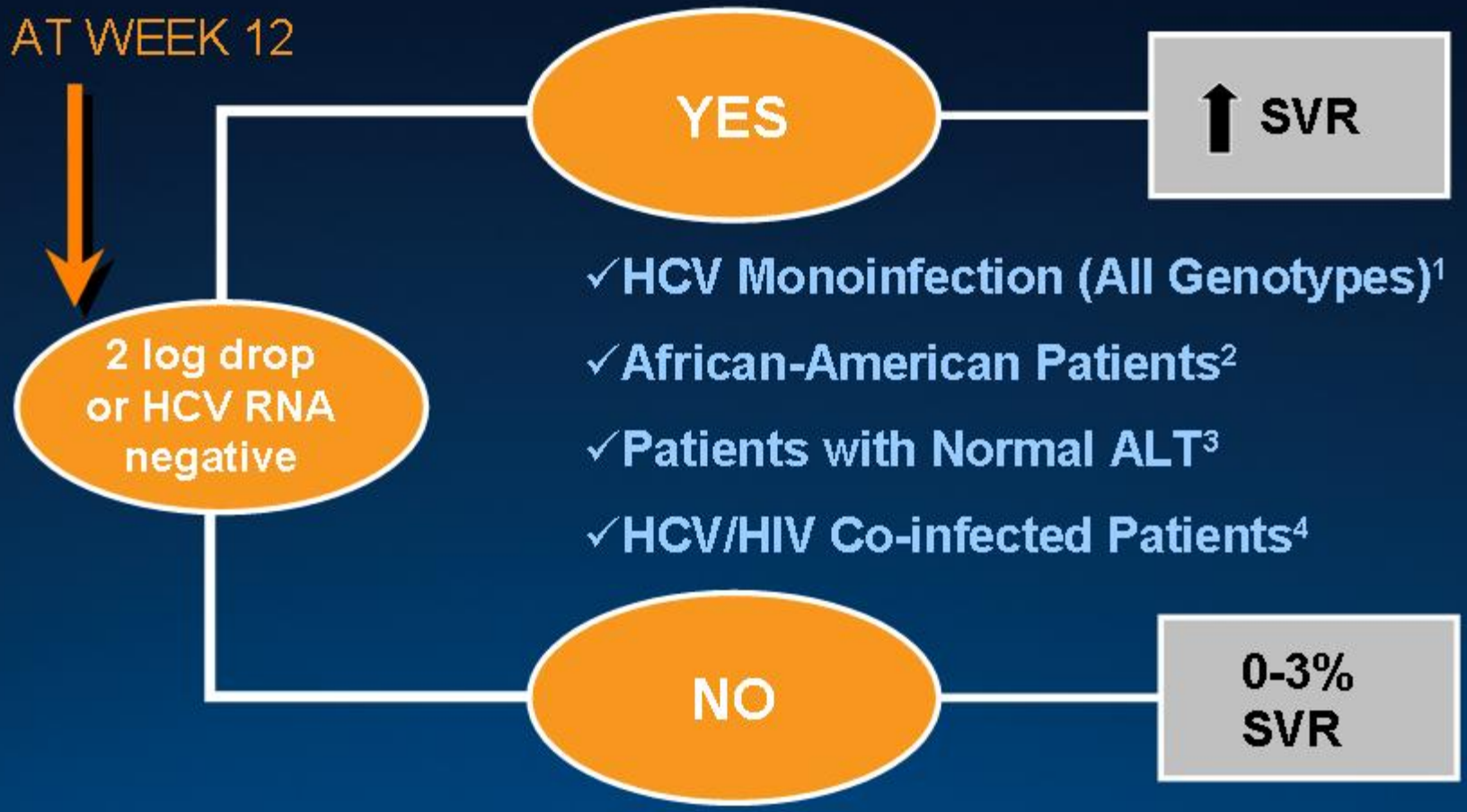
Shiffman M. *Current Gastroenterology Reports*. 2006;8:46-52.

Rate of Viral Decline Determines Period of HCV RNA Negativity



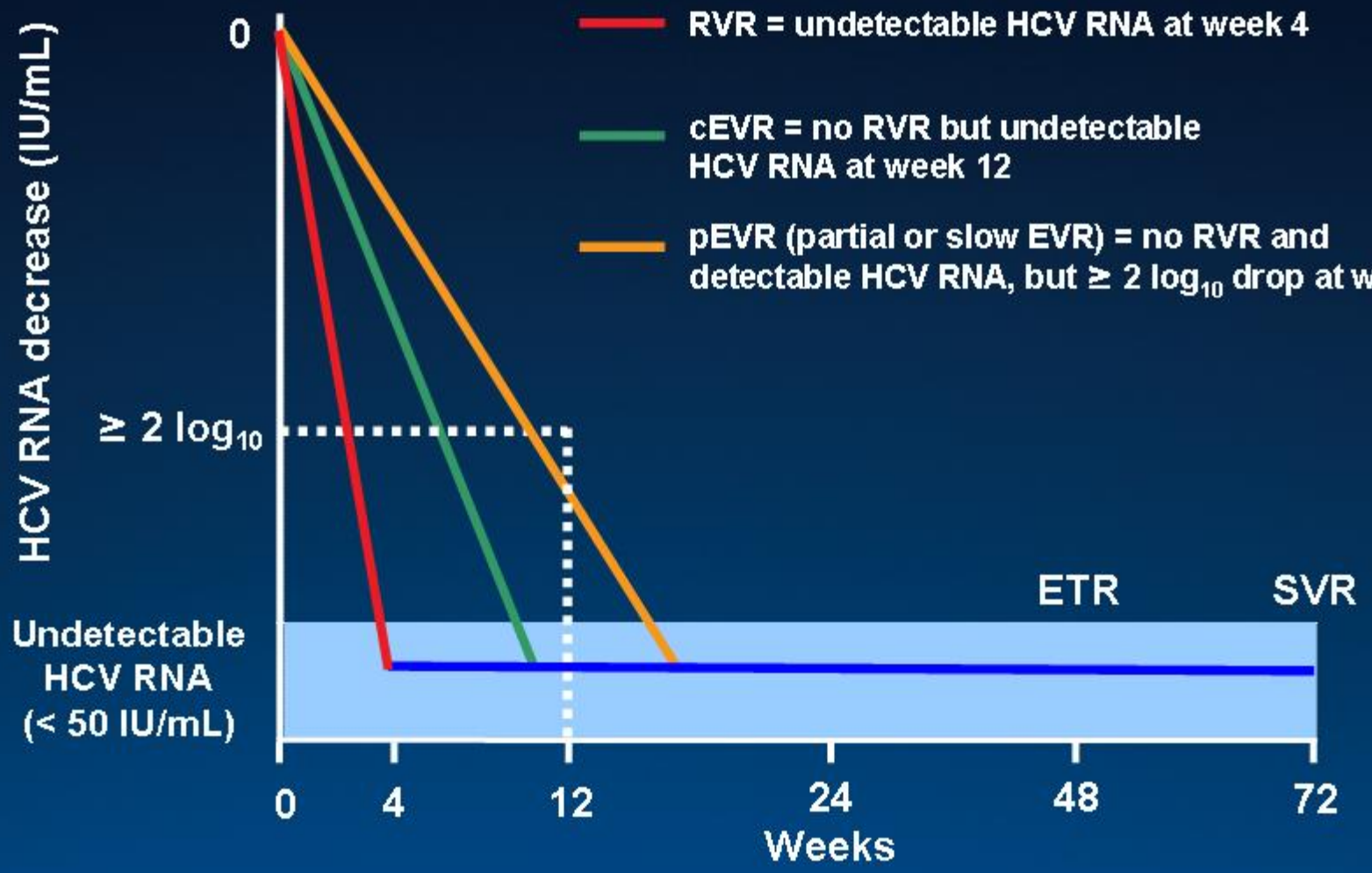
Darling JM, Fried MW. *Clin Liver Dis*. 2006;10:835-850.
Adapted from http://www.hepatitis.va.gov/vahep?page=prtop04-wp-03 accessed January 4th, 2008

Predictive Value of EVR Across Diverse Populations



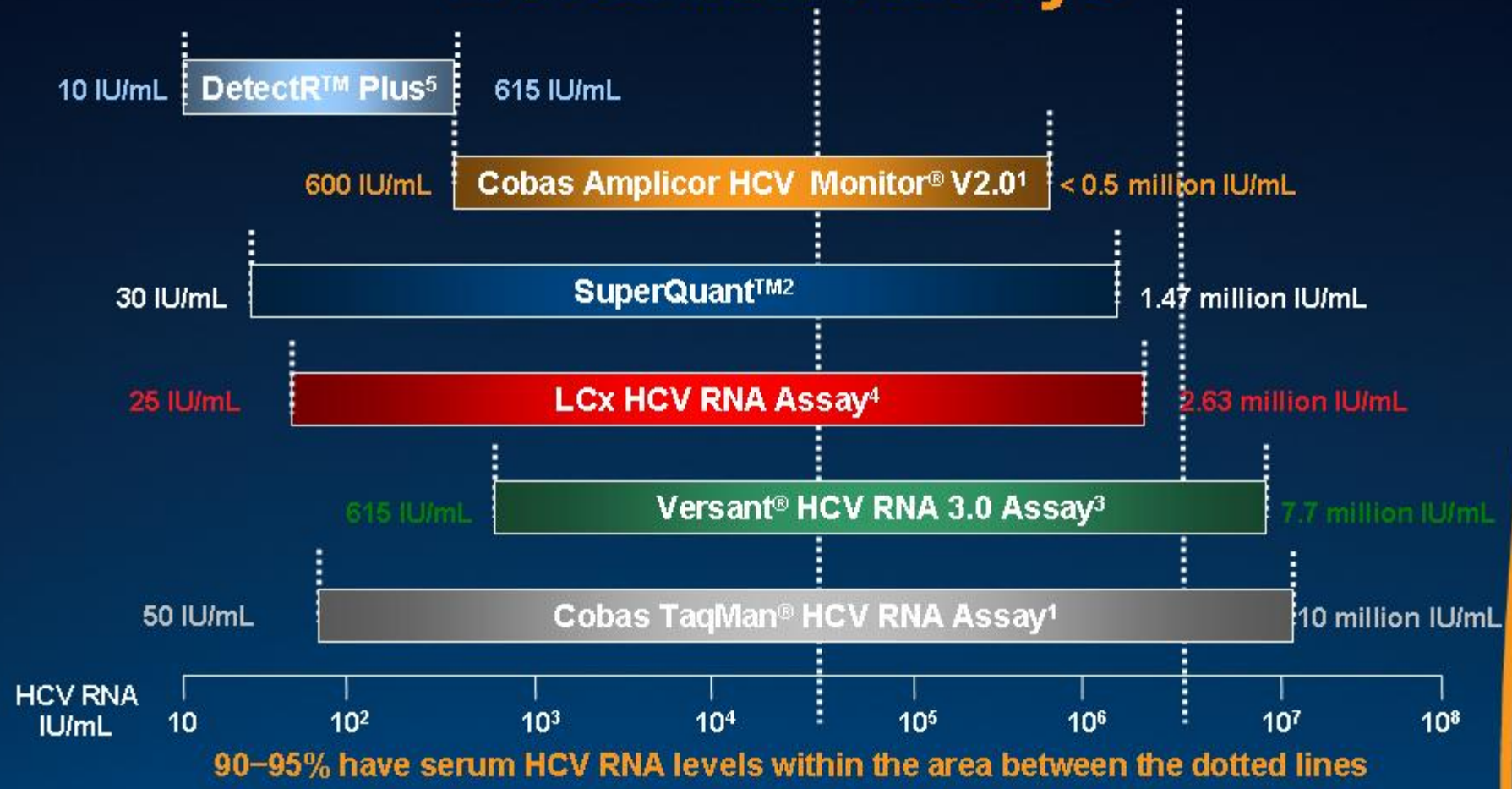
[1]Ferenci P. AASLD 2001, Nov. 9-13, Dallas, TX. Abstract 716.
[2]Jeffers LJ, et al. *Hepatology*. 2004;39:1702-1708.
[3]Zeuzem S, et al. *Gastroenterology*. 2004;127:1724-1732.
[4]Torriani FJ, et al. *N Engl J Med*. 2004;351:438-450.

Refining Definitions of Virological Response at Week 4 and Week 12



Sánchez-Tapias JM, et al. EASL 2007, April 11-15, Barcelona, Spain. Poster 641.

Quantification Range of HCV Viral Detection Assays



90–95% have serum HCV RNA levels within the area between the dotted lines

[1]Cobas Amplicor Monitor and Cobas Taqman are registered trademarks of a group of Hoffmann La-Roche Inc.; Available at: http://molecular.roche.com/diagnostics/virology/products_virology_11.html. Accessed December 6, 2007. [2]SuperQuant is a trademark of National Genetics Institute, a subsidiary of Labcorp Inc. Available at: www.ngi.com. Accessed December 6, 2007. [3]Versant is a registered trademark of Siemens. Available at: http://diagnosticssiemens.com. Accessed December 6, 2007. [4]Pawlotsky J-M. Use and interpretation of virological tests for hepatitis C. *Sem Liv Dis*. 2003;23:3-11. [5]DetectRTM Plus is a trademark of Specialty Laboratories. Available at: www.specialtylabs.com. Accessed April 9, 2007.

"Drugs don't work in patients who don't take them"

~ C. Everett Koop, MD

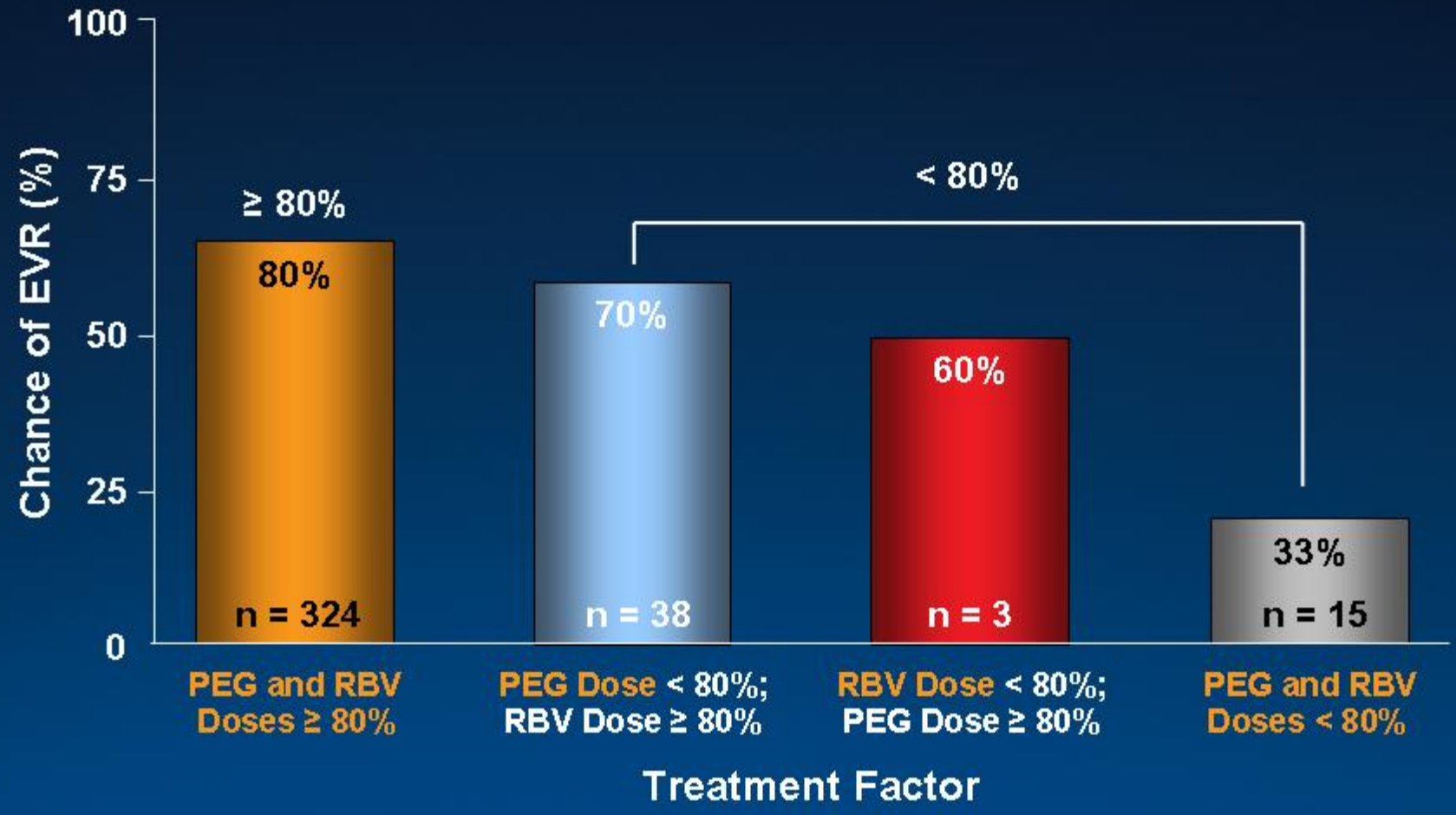
PEG-Intron™ and RBV Therapy Adherence and EVR: Study Overview

- Retrospective evaluation of data from Manns et al (2001) study to determine whether EVR could predict treatment outcome
- Patients randomization
  - PEG-Intron 1.5 mcg/kg/wk and RBV 800 mg/d (N = 511)
  - PEG-Intron 1.5 mcg/kg/wk and RBV 10.6 mg/kg/d (n = 174)
  - Interferon 3 MU TIW and RBV 1000/2000 mg/d (n = 505)
- Definition of adherent patients
  - Patients who received ≥ 80% of their total interferon dose, who received ≥ 80% of ribavirin dose and treated for ≥ 80% of expected duration on therapy

Davis GL, et al. *Hepatology*. 2003;38:645-652.

PEG-Intron and RBV Therapy: Adherence and EVR

PEG-Intron start dose: 1.5 mcg/kg each wk and RBV start dose: 800 mg/d



Davis GL, et al. *Hepatology*. 2003;38:645-652.

Ribavirin Exposure Predicts Virologic Response in Genotype 1 Patients

- Analysis of Pegasys Canadian Expanded Access program to examine the relationship of drug exposure to EVR and SVR
- Genotype 1, treatment naïve patients (n = 720)
- All patients treated with Pegasys 180 mcg/wk with either ribavirin 800 mg/day or 1000/1200 mg/day for 48 weeks
  - First phase of trial all patients received RBV 800 mg/day
  - Second phase increase RBV 1000/1200 mg/day per body weight based on updated trial information and guidelines
- Pegasys and ribavirin exposure and baseline prognostic factors were assessed in a multiple logistic regression
- No hematopoietic growth factors were used

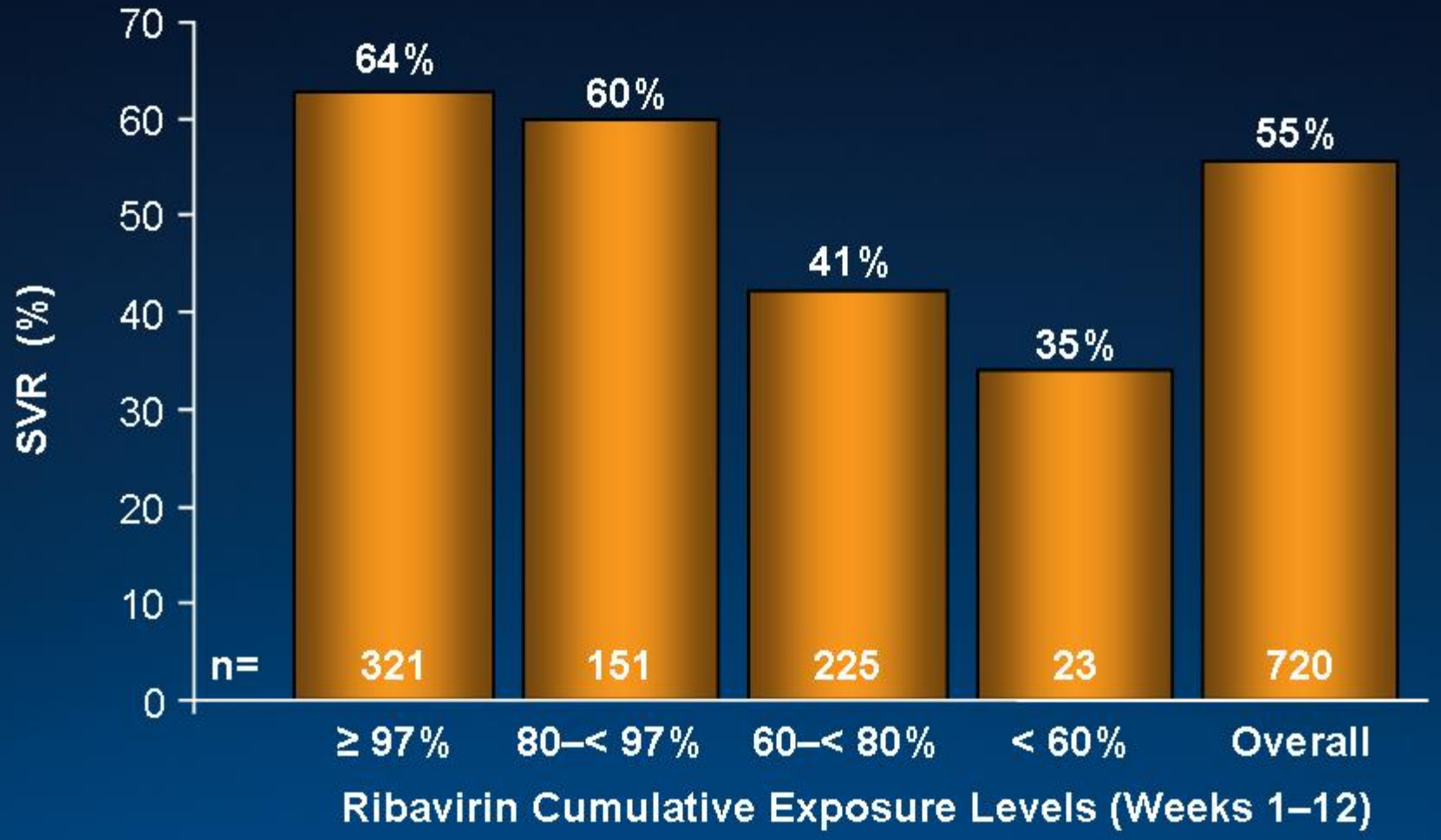
Bain VG, et al. Presented at AASLD. Oct 27-31, 2006. Boston, MA. Abstract.

Influence of Cumulative Copegus Exposure on SVR in Genotype 1: Study Overview

- Retrospective analysis of 569 genotype 1 patients from two 48 week phase III clinical trials treated with Pegasys 180 mcg/week and Copegus 1000–1200 mg/day
- Evaluated the effects of Pegasys and Copegus dose reductions and cumulative drug exposure on SVR
- Cumulative drug exposure = (total dose received – quantity returned) expressed as a percentage of planned total dose

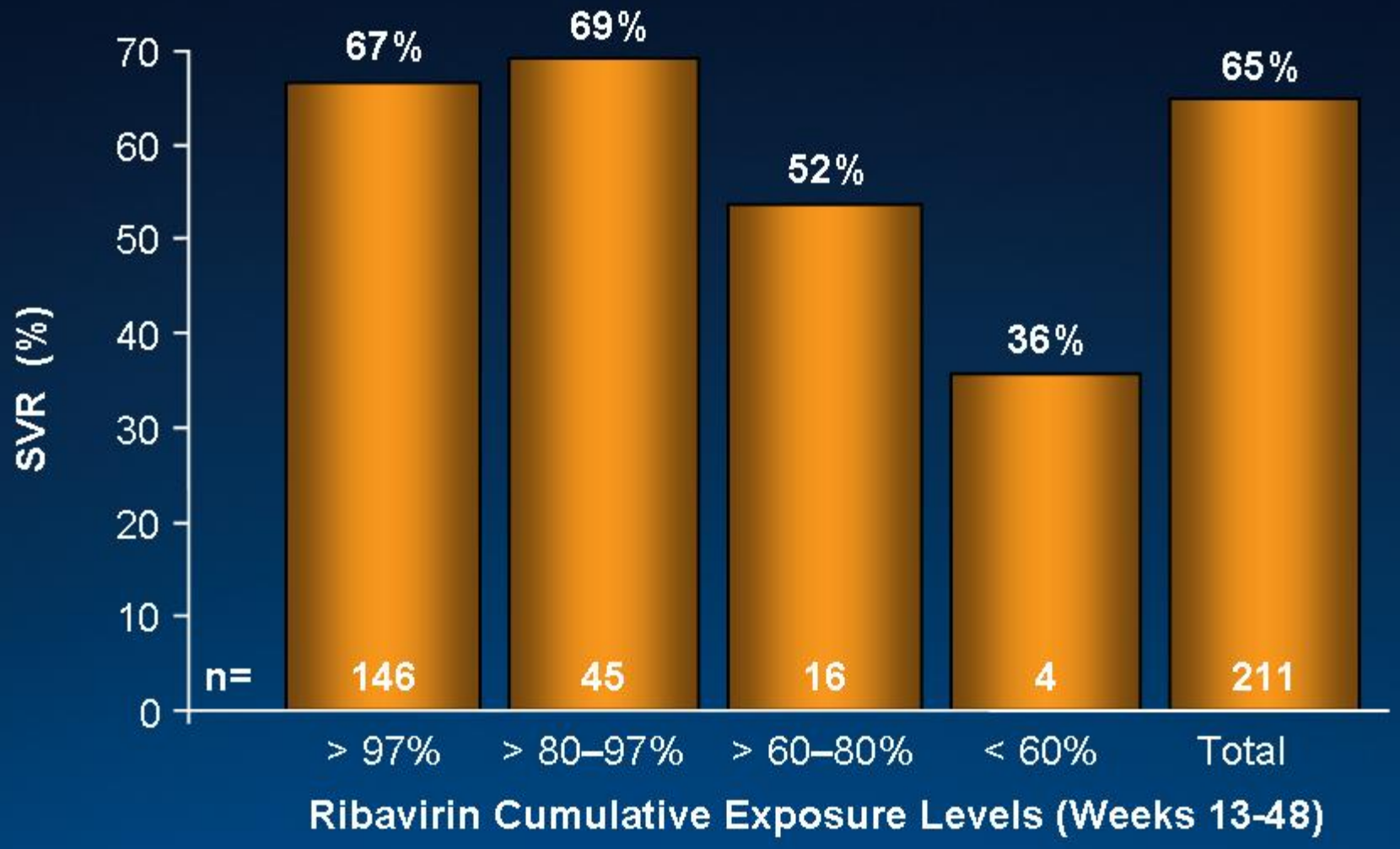
Reddy KR, et al. *Clin Gastroenterol Hepatol.* 2007;5:124-129.

Drug Exposure Predicts Virologic Response in Genotype 1 Patients



Bain VG, et al. Presented at AASLD. Oct 27-31, 2006. Boston, MA. Abstract.

Influence of Cumulative Copegus Exposure on SVR in Genotype 1: Weeks 13-48*



*Includes only patients with ≥ 97% ribavirin exposure during weeks 1–12

Reddy KR, et al. *Clin Gastroenterol Hepatol.* 2007;5:124-129.

Ribavirin Exposure Predicts Virologic Response in Genotype 1 Patients: Conclusions

- Ribavirin drug exposure significantly impacts the likelihood of achieving an EVR and SVR in genotype 1 patients
  - Impact was seen when analyzed by ribavirin dose group and calculated ribavirin mg/kg/day
- Ribavirin exposure was equally critical during weeks 1–12 and weeks 13–48 of treatment
- Impact of Pegasys cumulative exposure could not be assessed due to minimal dose reductions and discontinuations

Bain VG, et al. Presented at AASLD. Oct 27-31, 2006. Boston, MA. Abstract.

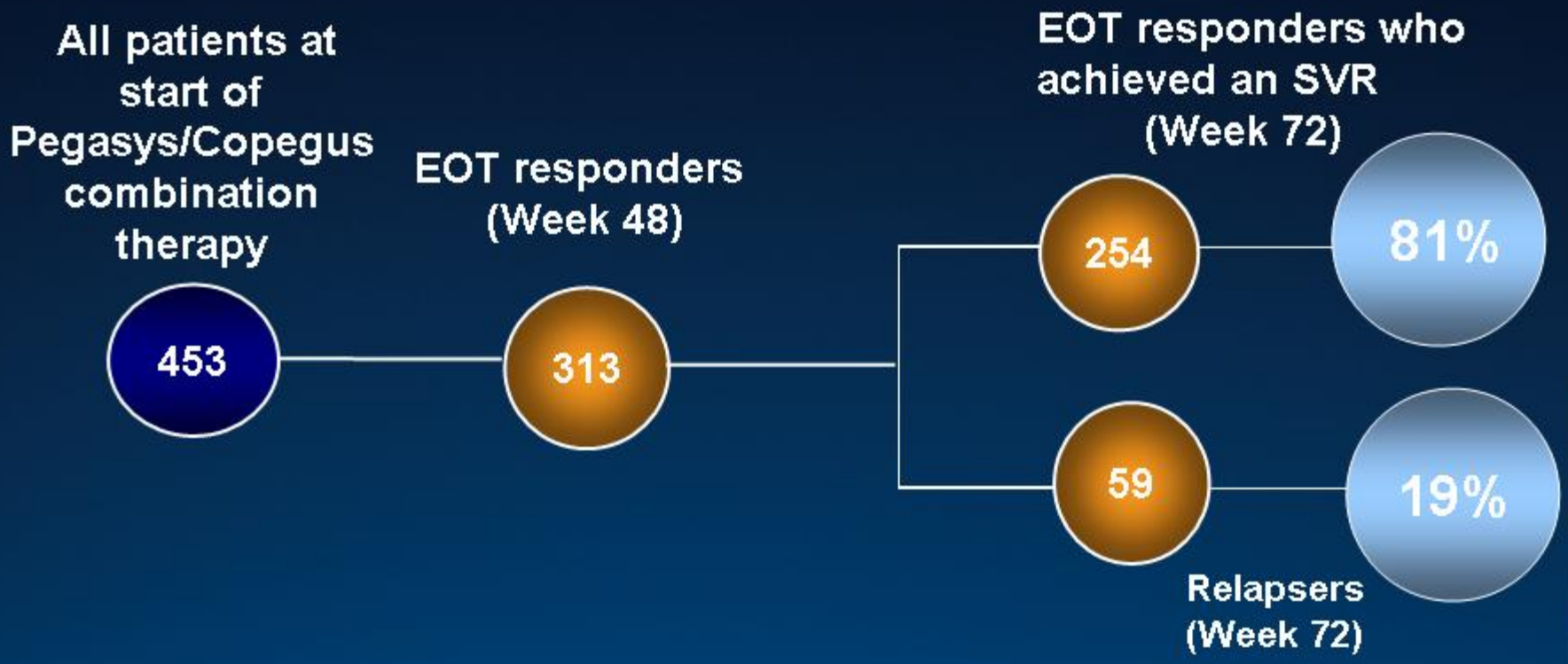
Virologic Response Guided Therapy

Predicting Relapse

Relapse Rates of Pegylated Interferons

- Relapse is a measure of the number of patients who have an end-of-treatment (EOT) response but do not subsequently achieve an SVR
- Definition of "relapse rate"
  - (ETR-SVR)/(ETR) x 100%
- Consistent and equivalent virologic definitions of SVR are critical for any comparisons of relapse rates of HCV therapies

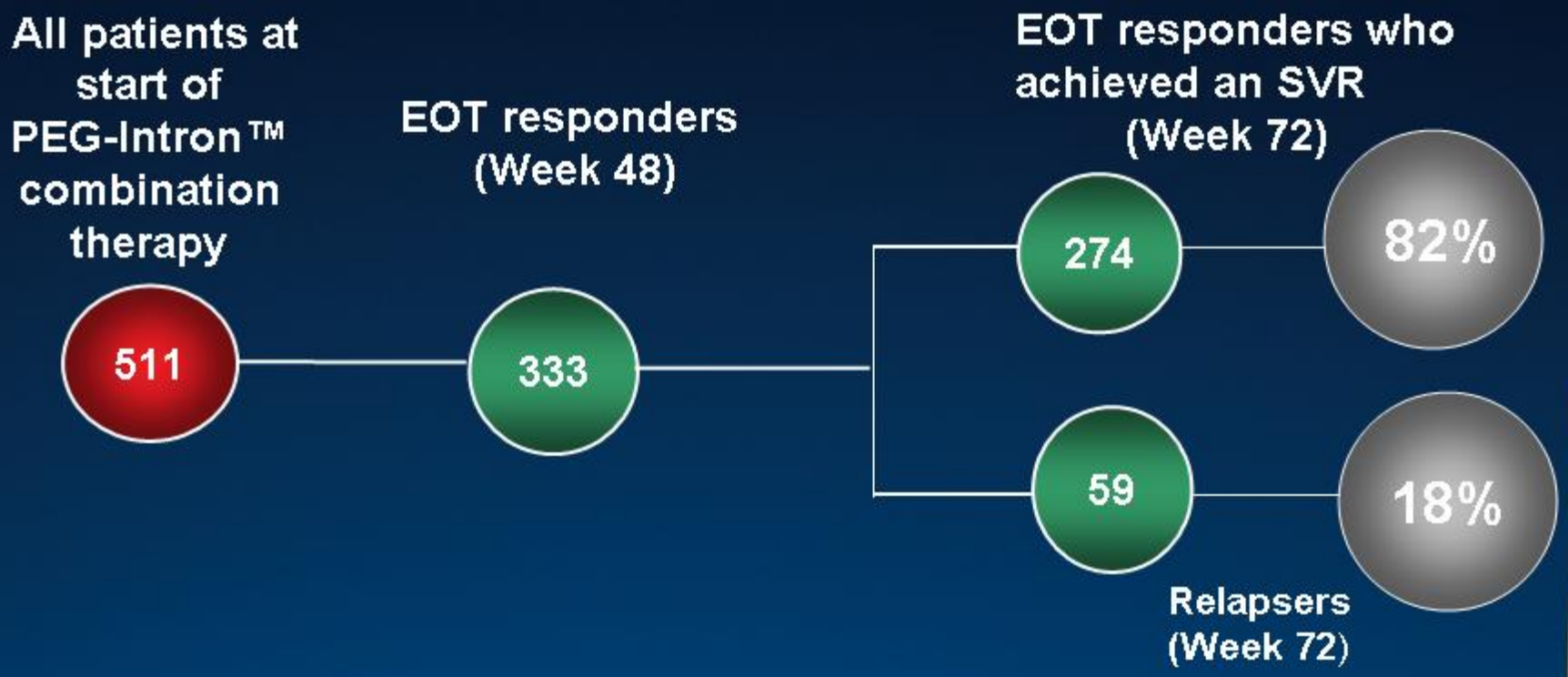
Relapse Rates for Pegasys



- 56% of all patients taking Pegasys in combination therapy with Copegus achieved an SVR versus 44% of patients taking Intron A plus ribavirin.

Calculated from: Fried MW, et al. *N Engl J Med*. 2002;347:975-982.

Relapse Rates for PEG-Intron



- 54% of all patients taking PEG-Intron (1.5 mcg/kg) combination therapy achieved an SVR (N = 274)

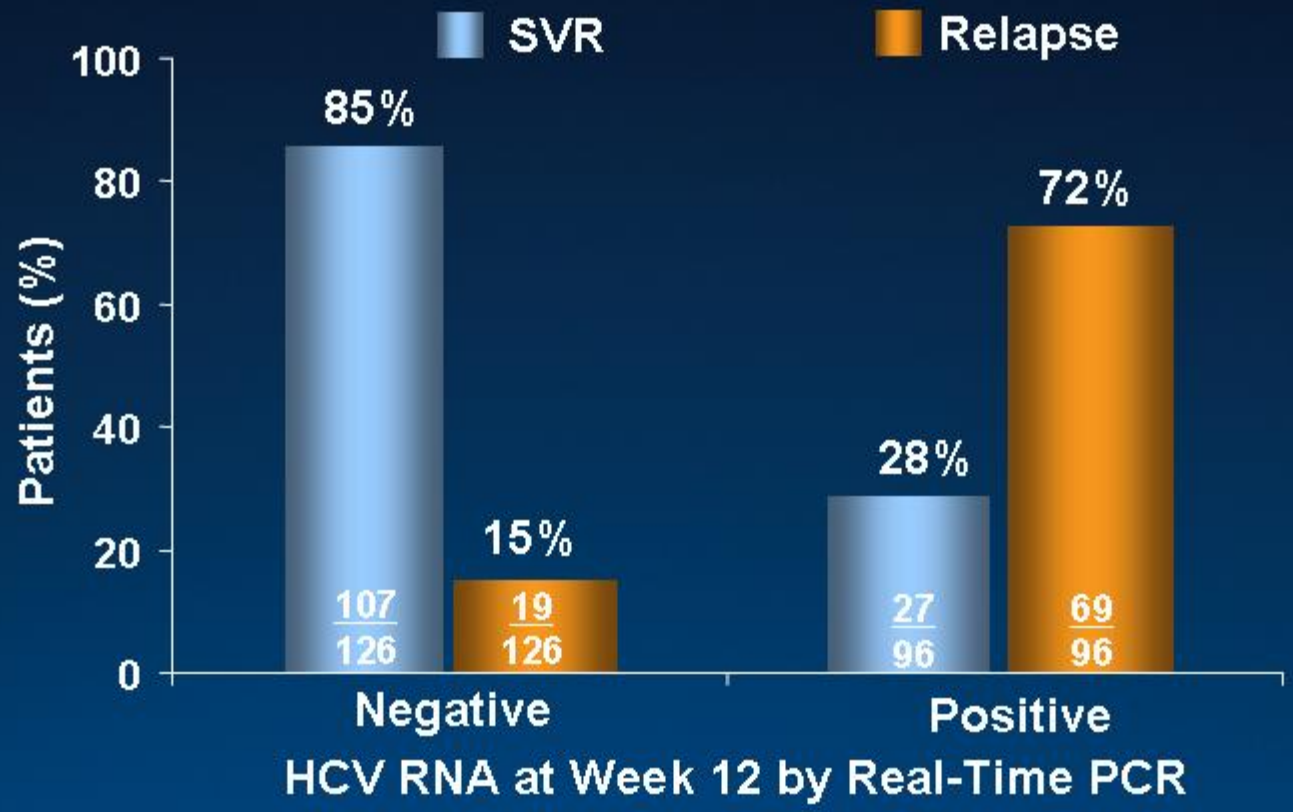
Manns M, et al. *Lancet*. 2001;358:958-965.

Minimal Residual Hepatitis C Viremia at Week 12 Predicts Type of Response: *Study Overview*

- Study evaluated whether minimal residual viremia predicts relapse in patients with EVR
  - Detection with Roche Cobas TaqMan, lower limit of detection 10 IU/mL
- Analysis of week 12 HCV viral kinetics and later response in patients receiving pegylated interferon (either Pegasys or PEG-Intron) and ribavirin
  - N = 773 treatment-naïve genotype 1 patients

Bergk A, et al. DDW 2006, May 20-25, Los Angeles, CA. Research Abstract 176.

Minimal Residual Hepatitis C Viremia at Week 12 Predicts Type of Response



Roche Cobas TaqMan, lower limit of detection 10 IU/mL.

Bergk A, et al. DDW 2006, May 20-25, Los Angeles, CA. Research Abstract 176.

Viral Response Guided Therapy: *Conclusions*

- Baseline host and viral factors have often been the focus of predicting response to treatment
  - Therapy has only been modified for genotype
- On-treatment HCV RNA levels at week 4 and week 12 are simple and reliable tools for predicting response
- Combining on-treatment HCV RNA level detection with consideration of host and viral factors associated with poor prognosis can be used to optimize HCV treatment outcomes

Minimal Residual Hepatitis C Viremia at Week 12 Predicts Type of Response: *Study Overview*

- Study evaluated whether minimal residual viremia predicts relapse in patients with EVR
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Bergk A, et al. DDW 2006, May 20-25, Los Angeles, CA. Research Abstract 176.

Virologic Response Guided Therapy

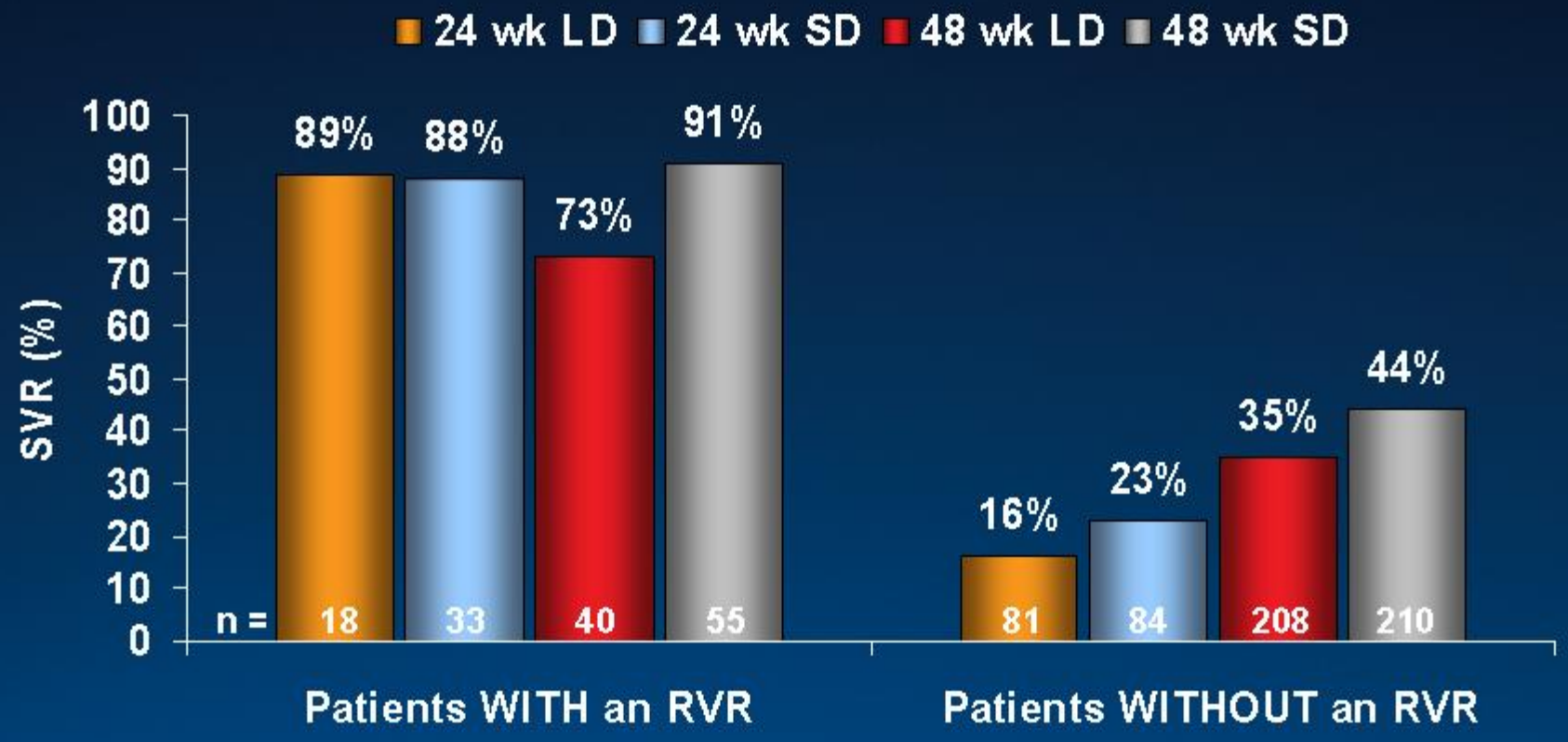
Genotype 1

Pegasys and Copegus: G1 Rapid Virologic Responders

- Retrospective analysis of patients treated in Pegasys and Copegus Phase III trial evaluating duration of therapy and RBV dose
- Population (N = 729)
  - Treatment naïve
  - Genotype 1
  - Received at least 1 dose of drug and 4 week RNA available
- Logistic regression analysis performed to evaluate the prognostic value of RVR for SVR

Jensen D, et al. *Hepatology*. 2006;43:954-960.

Pegasys and Copegus: G1 Rapid Virologic Responders



LD = low dose (RBV 800 mg/d)
SD = standard dose (RBV 1000/1200 mg/d)

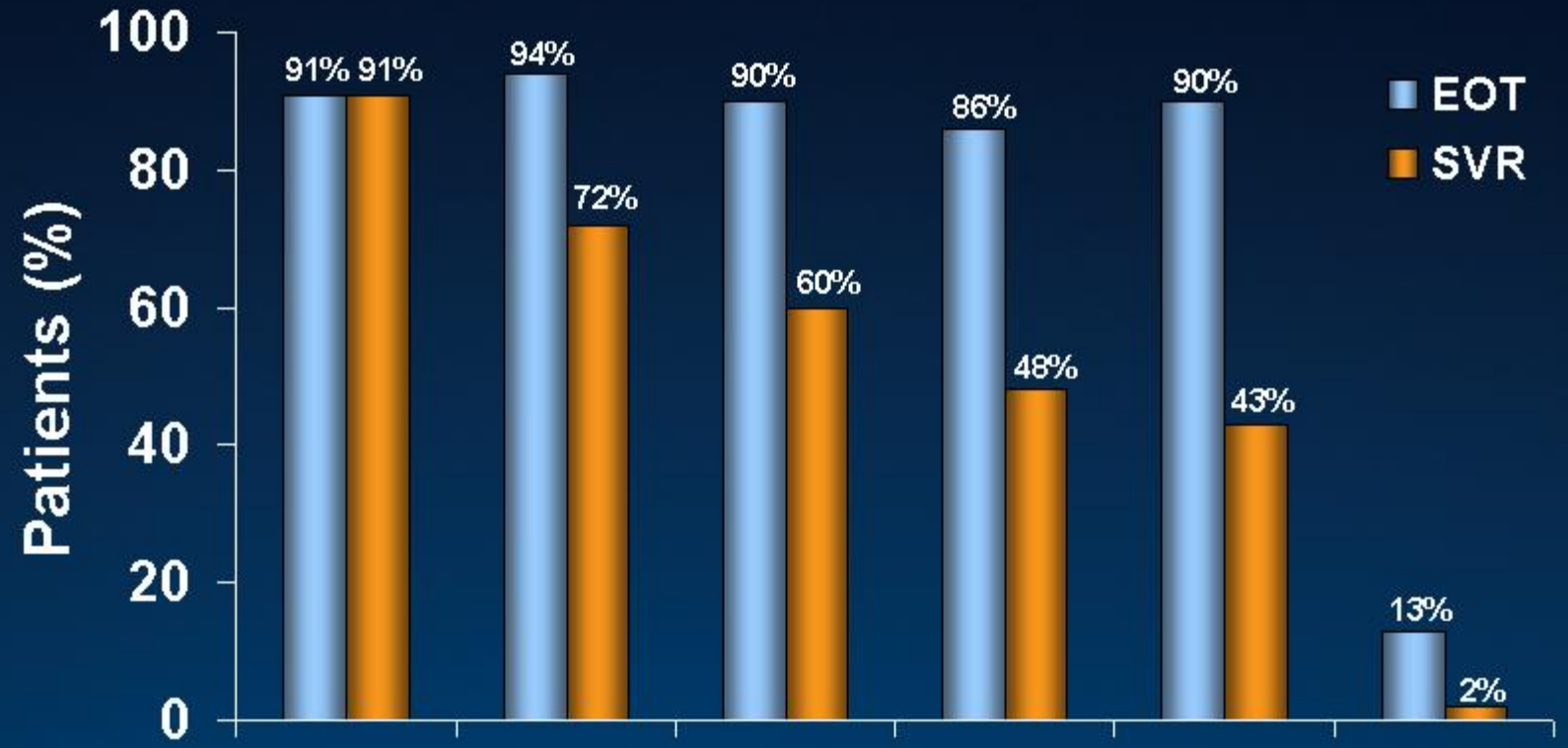
Jensen D, et al. *Hepatology*. 2006;43:954-960.

Pegasys and Copegus: G1 Rapid Virologic Responders *Conclusions*

- In this retrospective analysis of genotype 1 patients (N = 729), analysis of rapid clearance of HCV RNA revealed that an RVR significantly increased the probability of an SVR
- Early clearance of HCV RNA increased the likelihood of an end-of-treatment response and reduced the likelihood of virological relapse during follow-up
- There was no significant difference in SVR rates in patients who were treated for 24 or 48 weeks and who reached RVR at 4 weeks

Jensen D, et al. *Hepatology*. 2006;43:954-960.

Predicting SVR in G1 Patients Treated With Pegasys and Copegus



HCV RNA Status							
	Wk 4	Neg	> 2 Log	< 2 Log	> 2 Log	< 2 Log	Any
	Wk 12	Neg	Neg	Neg	> 2 Log	> 2 Log	Any
	Wk 24	Neg	Neg	Neg	Neg	Neg	Pos

Ferenci P, et al. *J Hepatol.* 2005;43:425-433.

Predicting SVR With an RVR or an EVR: *Study Overview*

- Analysis of data from genotype 1 patients from a total of 6 randomized, multicenter studies (N = 1,685)
- The 6 studies evaluated Pegasys 180 mcg/wk and ribavirin for 48 weeks[1-6]
  - Daily dose of ribavirin varied across the 6 studies
  - SVR was consistently defined as undetectable HCV RNA (< 50 IU/mL by qualitative PCR assay) at the end of a 24-week untreated follow-up period
- Definitions of viral response
  - RVR: undetectable HCV RNA (< 50 IU/mL) at week 4
  - EVR: undetectable HCV RNA at week 12 in patients without an RVR

[1.] Ferenci P, et al. *J Hepatol*. 2005;43:425-433. [2.] Hadziyannis S, et al. *Ann Intern Med*. 2004;140:346-355. [3.] Berg T, et al. *Gastroenterology*. 2006;130:1086-1097. [4.] Sánchez-Tapias JM, et al. *Gastroenterology*. 2006;131:451-460. [5.] Bronowicki JP, et al. *Gastroenterology*. 2006;131:1040-1048. [6.] Sakai T, et al. *J Hepatol*. 2006;44(suppl2):S224-S225.

Marcellin P, et al. EASL 2007, April 11-15, Barcelona, Spain. Poster 613.

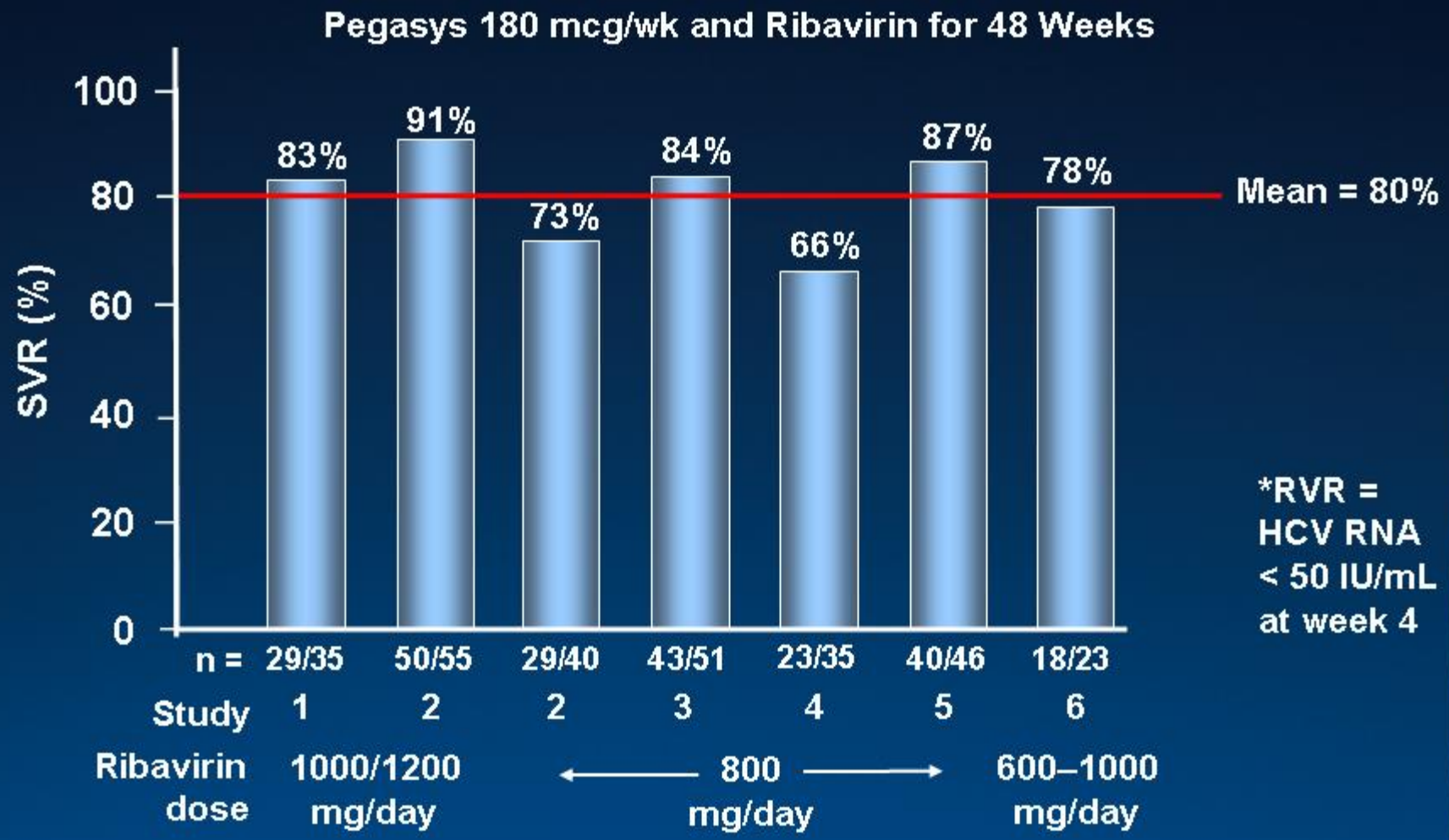
Rates of RVR and EVR in G1 Patients Treated With Pegasys and Copegus

	48 weeks of treatment with Pegasys 180 mcg and		
	RBV 800 mg (4 studies)[1-4] n = 1,019	RBV 1000/ 1200 mg (2 studies)[1,5] n = 569	RBV 600–1000 mg (1 study)[6] n = 97
RVR	16–27%	12–20%	24%
EVR	34–52%	40–44%	52%

RVR = **R**apid **V**irological **R**esponse
EVR = **E**arly **V**irological **R**esponse

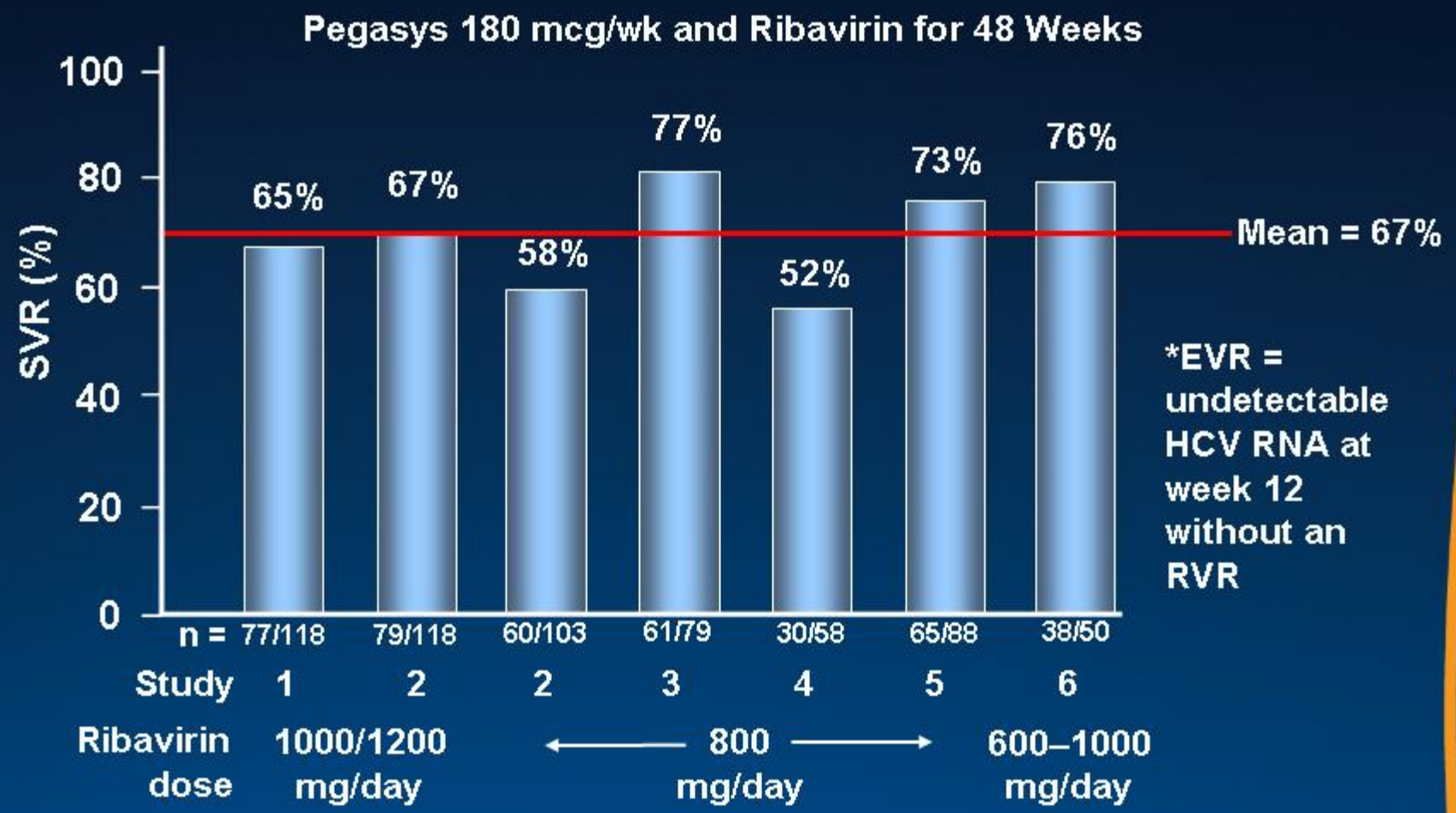
[1-6] Refer to slide notes for complete study references
Marcellin P, et al. EASL 2007, April 11-15, Barcelona, Spain. Poster 613.

Predicting SVR in G1 Patients With an RVR*



Marcellin P, et al. EASL 2007, April 11-15, Barcelona, Spain. Poster 613.

Predicting SVR in G1 Patients With an EVR*



Marcellin P, et al. EASL 2007, April 11-15, Barcelona, Spain. Poster 613.

Predicting SVR With an RVR or an EVR: *Conclusion*

- Genotype 1 patients treated with 48 weeks of Pegasys and Copegus who achieve RVR or EVR have a high probability of achieving SVR
- On-treatment HCV RNA levels at week 4 and 12 are strong predictors of response
- Use of higher ribavirin doses appears to result in higher SVR rates among patients with both RVR and EVR, although uncontrolled factors could be contributing to this effect

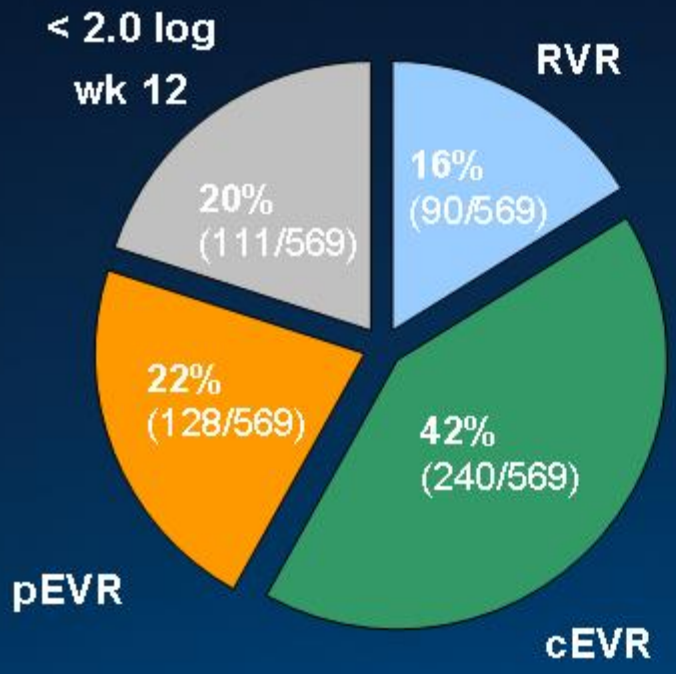
Marcellin P, et al. EASL 2007, April 11-15, Barcelona, Spain. Poster 613.

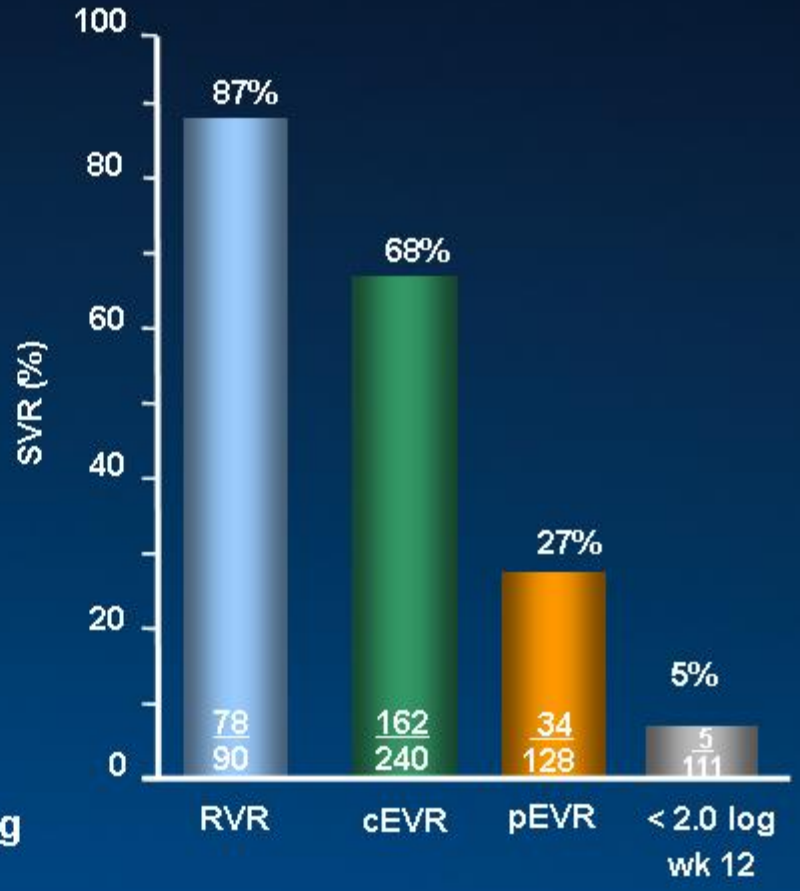
New Definitions of Virologic Response to Antiviral Therapy for Hepatitis C

Response	Definition
RVR Rapid Virologic Response	HCV RNA negative at 4 weeks as defined by HCV RNA < 50 IU/mL
EVR Early Virologic Response	HCV RNA negative or > 2 $\log_{10}$ drop at week 12
– **Complete EVR (cEVR)**	No RVR but HCV RNA negative (< 50 IU/mL) at week 12
– **Partial EVR (pEVR)**	No RVR and detectable but ≥ 2 $\log_{10}$ drop in HCV RNA at week 12
• **Slow responder**	≥ 2 $\log_{10}$ drop in HCV-RNA at week 12 but not HCV RNA negative until week 24
• **Partial responder**	> 2 $\log_{10}$ drop in HCV-RNA at week 12 but HCV RNA positive at week 24
SVR Sustained Virologic Response	HCV RNA negative 24 weeks after end of treatment
Relapse	HCV RNA negative at end of treatment but HCV RNA positive after treatment stopped

Ferenci P, et al. Presented at EASL 2006, April 26-30, Vienna, Austria. Abstract 8.
Marcellin P, et al. AASLD 2007, Oct. 2-6, Boston, MA. Poster 1308.
Sánchez-Tapias JM, et al. EASL 2007, April 11-15, Barcelona, Spain. Poster 641.
Paulon E, Naoumov NV. *Eur J Gastroenterol Hepatol*. 2006;18(4):321-325.
Pawlotsky JM. *Hepatology*. 2002;36(suppl 1):S65-S73.
Adapted from http://www.hepatitis.va.gov/vahep?page=prtop04-wp-03 accessed January 4th, 2008

Virologic Response and Predictors of SVR in G1 Patients Treated With Pegasys and Copegus





Retrospective review of phase 3 trials of Pegasys 180 mcg/wk and Copegus 1000/1200 mg for 48 weeks

Marcellin P, et al. AASLD 2007, Nov. 2-6, Boston, MA. Poster 1308.
Data on file (Reference #099-167). Hoffmann-La Roche Inc., Nutley, NJ.

The Near Future

Specifically Targeted Anti-viral Therapies for hepatitis C (STAT-C)